SEVENTH EDITION

PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

Howard C. Ansel, Ph.D.
Professor and Dean Emeritus
College of Pharmacy
The University of Georgia

Loyd V. Allen, Jr., Ph.D.
Professor Emeritus
College of Pharmacy
University of Oklahoma, and
Editor-in-Chief
International Journal of Pharmaceutical Compounding

Nicholas G. Popovich, Ph.D.
Professor and Associate Head
Department of Pharmacy Practice
School of Pharmacy and Pharmacal Sciences
Purdue University

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NEW DRUG DEVELOPMENT AND APPROVAL PROCESS

Chapter at a Glance

THE FEDERAL Food, Drug, and Cosmetic Act, as regulated through Title 21 of the U.S. Code of Federal Regulations, requires a new drug to be approved by the Food and Drug Administration (FDA) before it may be legally introduced in interstate commerce (1). The regulations apply to drug products manufactured domestically as well as those imported into the United States.

To gain approval for marketing, a drug's sponsor (e.g., a pharmaceutical company) must demonstrate, through supporting scientific evidence, that the new drug/drug product is safe and effective for its proposed use. The sponsor must also demonstrate that the various processes and controls used in producing the drug substance and in manufacturing, packaging, and labeling the drug product

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are properly controlled and validated, to ensure the production of a product that meets established standards of quality.

The process and time-course from drug discovery to approval for marketing can be lengthy and tedious, but are well defined and understood within the pharmaceutical industry. A schematic representation of the process for new drug development is shown in Figure 2.1 and the usual time-course is depicted in Figure 2.2. After the discovery (e.g., synthesis) of a proposed new drug, the agent is biologically characterized for pharmacologic and toxicologic effects and for potential therapeutic application. Preformulation studies are initiated to define the physical and chemical properties of the agent. Formulation studies follow, to develop the initial features of the proposed pharmaceutical product or dosage form. To obtain the required evidence that will demonstrate the drug's safety and effectiveness for its proposed use, a carefully designed and progressive sequence of preclinical (e.g., cell culture, whole animal) and clinical (human) studies are undertaken.

Only when the preclinical studies demonstrate adequate safety and the new agent shows promise as a useful drug will the drug's sponsor file an Investigational New Drug Application (IND) with the FDA for initial testing in humans. If the drug demonstrates adequate safety in these initial human studies, termed Phase 1, progressive human trials through Phases 2 and 3 are undertaken to assess both safety and efficacy. As the clinical trials progress, laboratory work continues toward defining the agent's basic and clinical pharmacology and toxicology, product design and development, manufacturing scale-up and process controls, analytical methods development, proposed labeling and package design, and initial plans for marketing. At the completion of the carefully designed preclinical and clinical studies, the drug's sponsor may file a New Drug Application (NDA) seeking approval to market the new product.

The FDA's approval of an NDA indicates that the body of scientific evidence submitted sufficiently demonstrates that the drug/drug product is safe and effective for the proposed clinical indications; that there is adequate assurance of its proper manufacture and control; and that the final labeling accurately presents the necessary information for its proper use.

The content of a product's approved labeling, represented by the package insert, is a summary of the entire drug development process because it contains the essential chemistry, pharmacology, toxicology, indications and contraindications for use, adverse effects, formulation composition, dosage, and storage requirements, as ascertained during the research and development process.

In addition to the general new drug approval process, special regulations apply for the approval of certain new drugs to treat serious or life-threatening illnesses, as AIDS and cancer. These may be placed on an accelerated or "fast track" program for approval. Also, in instances in which there are no satisfactory approved-drug or treatment alternatives to treat a serious medical condition, special protocols may be issued permitting use of an investigational drug to treat some patients prior to approval of the NDA. This type of protocol is termed a "Treatment IND." Treatment INDs often are sought for "orphan drugs," which are targeted for small numbers of patients who have rare conditions or diseases for which there are no satisfactory alternative treatments.

For certain changes in a previously approved NDA, such as a labeling or formulation change, a manufacturer is required to submit for approval a Supplemental New Drug Application (SNDA).

An Abbreviated New Drug Application (ANDA) is used to gain approval to market a duplicate product (usually a competing generic product) to one that had been approved previously and marketed by the pioneer, or original sponsor, of the drug. In these instances, the sponsor of the ANDA provides documentation on the chemistry, manufacturing, controls, and bioavailability of the proposed product to demonstrate biologic equivalency to the original product (2). Clinical data on the drug's safety and efficacy are not required because clinical studies were previously provided by the pioneer sponsor.

Federal regulations are varied and specific for antibiotic drugs (3); for biologics, such as human blood products and vaccines, which require approval of a Biologics Licensing Application (BLA) for distribution (4); for OTC drugs (5); and for animal drugs, which may require an Investigational New Animal Drug Application (INADA), a New Animal Drug Application (NADA) or a Supplemental New Animal Drug Application (SNADA) (6). Medical devices, such as catheters and cardiac pacemakers, follow a separate premarket approval process as defined in the Code of Federal Regulations (7).

The following sections are intended to serve as an overview of the new drug development and approval process. More specific and detailed information may be obtained directly from the referenced sections of the Code of Federal Regulations (1–7), from relevant entries in the Federal Register (8), and from other treatises on the topic (9–13).

New Chemical Entity
sources:
- Organic Synthesis
- Molecular Modification
- Isolation from Plants

Preclinical Studies
including:
- Chemistry
- Physical Properties
- Biological
  - Pharmacology
  - ADME
  - Toxicology
- Preformulation

Investigational New Drug Application (IND)
- Submission
- FDA Review

Clinical Trials
- Phase I
- Phase II
- Phase III

Preclinical Studies *(continued)*
plus:
- Long-term Animal Toxicity
- Product Formulation
- Manufacturing and Controls
- Package and Label Design

New Drug Application (NDA)
- Submission
- FDA Review
- Pre-approval Plant Inspection
- FDA Action

Postmarketing
- Phase IV Clinical Studies
  - Clinical Pharmacology / Toxicology
  - Additional Indications
- Adverse Reaction Reporting
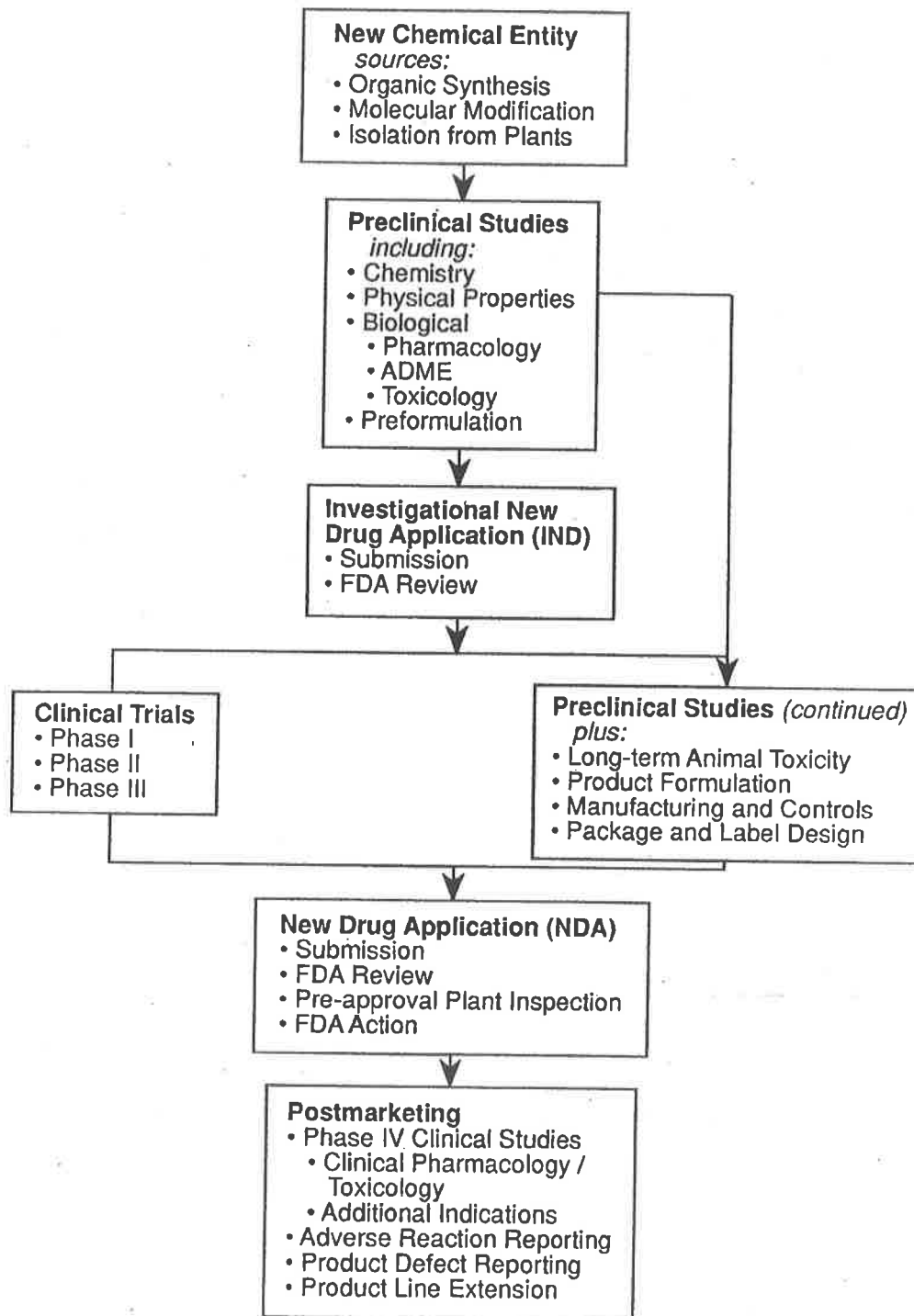- Product Defect Reporting
- Product Line Extension

Fig. 2.1   *Schematic representation of the new drug development process, from drug discovery, through preclinical and clinical studies, FDA review of the new drug application, and postmarketing activities.*

Pre-Clinical Research and Development	Clinical Research and Development	NDA Review	Post-Marketing Surveillance
Initial Synthesis and Characterization	Phase 1		Adverse Reaction Reporting
	Phase 2		
	Phase 3		Surveys / Sampling Testing
Animal Testing Short-Term Long-Term			Inspections
Average 6½ years	Average 7 years	Average 1½ years	
FDA 30-Day Safety Review		NDA Submitted	NDA Approved

Average of Approx 15 years from initial synthesis to approval of NDA

Fig. 2.2 *Time course for the development of a new drug. (Adapted from FDA Consumer, 21:5, 1987 and New Drug Approvals in 1997, Pharmaceutical Research and Manufacturers Association, January, 1998.)*

Drug Discovery and Drug Design

The discovery of new drugs and their development into commercial products takes place across the broad scope of the pharmaceutical industry. The basic underpinning for this effort is the cumulative body of scientific and biomedical information generated worldwide in research institutes, academic centers, and industry. The combined efforts of chemists, biologists, molecular biologists, pharmacologists, toxicologists, statisticians, physicians, pharmacists and pharmaceutical scientists, engineers, and many others are involved in the drug discovery and development process.

Some pharmaceutical firms focus their research and development (R&D) activities on new prescription drugs for human use, whereas other firms concentrate on the development of OTC medications, generic drugs, biotechnology products, animal health-care drugs, diagnostic products, and/or medical devices. Many of the large pharmaceutical companies develop and manufacture products of various types, with some firms having subsidiary companies for specialized functions and products.

The pharmaceutical industry in the United States grew rapidly during World War II and in the years immediately following. The upsurge in the domestic production of drugs and pharmaceutical products stemmed in part from the wartime hazards and consequent undependability of overseas shipping, the unavailability of drugs from previous sources, and the increased need for drugs of all kinds, but especially those with life-saving capabilities. One such drug is penicillin, the antibiotic which became commercially available in 1944, 15 years after its discovery in England by Sir Alexander Fleming and 1 year before the end of the war.

After the war, other antibiotics were developed and today there is a host of them, with effectiveness against a range of pathogens. The postwar boom in drug discovery continued with the development of

many new agents, as vaccines to protect against poliomyelitis, measles, and influenza, and new pharmacologic categories of drugs including oral hypoglycemic drugs effective against certain types of diabetes mellitus, antineoplastic or anticancer drugs, immunosuppressive agents which assist the body's acceptance of organ transplants, oral contraceptives to prevent pregnancy, and a host of tranquilizers and antidepressant drugs to treat the emotionally distressed.

In recent years, many new and important innovative therapeutic agents have been developed and approved by the FDA, including drugs to treat: acquired immune deficiency syndrome, AIDS (indinavir, Crixivan); refractory benign prostatic hyperplasia (finasteride, Proscar); migraine headaches (sumatriptan, Imitrex); ovarian carcinoma (paclitaxel, Taxol); gastric ulcers (cimetidine, Tagamet); hyperlipidemia (gemfibrozil, Lopid); hypertension (enalapril, Vasotec); congestive heart failure (carvedilol, Coreg); coronary artery disease (fluvastatin, Lescol); obsessive compulsive disorders (fluoxetine, Prozac); arthritis (nedocromil, Tilade); osteoporosis (alendronate, Fosamax); male impotence (sildenafil citrate, Viagra), infectious disease (ciprofloxacin, Cipro); and other diseases and conditions, with literally hundreds of potential therapeutic agents in various stages of clinical evaluation. Annually, approximately 40 new molecular entities (NME) receive FDA approval for marketing. In addition, many new dosage strengths and dosage forms of previously approved drugs, new generic products, and new biologics are approved each year.

Not all drugs are discovered, developed, and first approved in the United States. There are many pharmaceutical companies involved in drug research and development in other countries and many drugs are first marketed abroad. Many of the world's largest pharmaceutical companies are multinational firms and have facilities for research and development, manufacturing, and distribution in countries around the world. Irrespective of country of origin, a drug may be proposed by its sponsor for regulatory approval for marketing in the United States and/or in other countries. These approvals do not occur simultaneously, as they are subject to the laws, regulations, and requirements peculiar to each country's governing authority. However, the international effort to harmonize regulations through the work of the International Conference on Harmonization (ICH) as described at the end of this chapter fosters multinational drug approvals.

Sources of New Drugs

New drugs may be discovered from a variety of natural sources or created synthetically in the laboratory. They may be discovered by accident or as the result of many years of tireless pursuit.

Throughout history, plant materials have served as a reservoir of potential new drugs. Yet, only a small portion of the approximate 270,000 known plants thus far have been investigated for medicinal activity. Certain major contributions to modern drug therapy may be attributed to the successful conversion of botanic folklore remedies into modern wonder drugs. The chemical reserpine, a tranquilizer and hypotensive agent, is an example of a medicinal chemical isolated by design from the folklore remedy *Rauwolfia serpentina*. Another plant drug, periwinkle or *Vinca rosea*, was first scientifically investigated as a result of its reputation in folklore as an agent useful in the treatment of diabetes mellitus. Plant extractives from *Vinca rosea* yielded two potent drugs, which when screened for pharmacologic activity surprisingly exhibited antitumor capabilities. These two materials, vinblastine and vincristine, since have been used successfully in the treatment of certain types of cancer including acute leukemia, Hodgkin's disease, lymphocytic lymphoma, and other malignancies. Another example, paclitaxel (Taxol), prepared from an extract from the Pacific yew tree, is used in the treatment of ovarian cancer.

After the isolation and structural identification of active plant constituents, organic chemists may recreate them by total synthesis in the laboratory or more importantly use the natural chemical as the starting material in the creation of slightly different chemical structures through molecule manipulation procedures. The new structures, termed semisynthetic drugs, may have a slightly or vastly different pharmacologic activity than the starting substance, depending on the nature and extent of chemical alteration. Other plant constituents that in themselves may be inactive or rather unimportant therapeutically may be chemically modified to yield important drugs with profound pharmacologic activity. For example, the various species of *Dioscorea*, popularly known as Mexican yams, are rich in the chemical *steroid structure* from which cortisone and estrogens are semisynthetically produced.

Animals have served humans in their search for drugs in a number of ways. They not only have yielded to drug testing and biologic assay procedures but also have provided drugs that are mannered from their tissues or through their biologic

processes. Hormonal substances such as thyroid extract, insulin, and pituitary hormone obtained from the endocrine glands of cattle, sheep, and swine are lifesaving drugs used daily as replacement therapy in the human body. The urine of pregnant mares is a rich source of estrogens. Knowledge of the structural architecture of the individual hormonal substances has produced a variety of synthetic and semisynthetic compounds with hormone-like activity. The synthetic chemicals used as oral contraceptives are notable examples.

The use of animals in the production of various biologic products, including serums, antitoxins, and vaccines, has been of lifesaving significance ever since the pioneering work of Dr. Edward Jenner on the smallpox vaccine in England in 1796. Today, the poliomyelitis vaccine is prepared in cultures of renal monkey tissue, the mumps and influenza vaccines in fluids of chick embryo, the rubella (German measles) vaccine in duck embryo, and the smallpox vaccine from the skin of bovine calves inoculated with vaccinia virus. New vaccines for diseases as AIDS and cancer are being developed through the use of cell and tissue cultures.

Today, we are witnessing a new era in the development of pharmaceutical products due to the advent of genetic engineering, the sub-microscopic manipulation of the "double helix," the spiral DNA chain of life. Through this process, will come more abundant and vastly purer antibiotics, vaccines, and yet unknown chemical and biological products to combat human disease.

There are two basic technologies that drive the genetic field of drug development; they are recombinant DNA (rDNA) and monoclonal antibody (MoAB) production (14–16). Common to each technique is the ability to manipulate and produce proteins, the building blocks of living matter. Proteins represent an almost infinite source of drugs. Made up of long chains of amino acids, their sequence and spatial configuration offer a staggering number of possibilities. Both recombinant DNA and monoclonal antibody production techniques influence cells in their ability to produce proteins.

The more fundamental of the two techniques is recombinant DNA. It can potentially produce almost any protein. Genetic material can be transplanted from higher species, such as humans, into a lowly bacterium. This so-called "gene splicing" can induce the lower organism to make proteins, it would not otherwise have made. Such drug products as human insulin, human growth hormone, hepatitis B vaccine, epoetin alpha, and interferon are being produced in this manner.

Whereas recombinant DNA techniques involve the manipulation of proteins within the cells of lower animals, monoclonal antibody production is conducted entirely within the cells of higher animals, including the patient. The technique exploits the ability of cells that have the potential to produce a desired antibody and stimulates an unending stream of pure antibody production. These antibodies then have the capacity to combat the specific target.

Monoclonal antibodies have an enormous potential to change the face of medicine and pharmacy in the next decade and applications for their use are already in progress. Diagnostically, for example, monoclonal antibodies are used in home pregnancy testing products. Their use ensures that a woman can perform the test easily, in a short period, with high reproducibility, and in an inexpensive manner. In these tests, the monoclonal antibody is highly sensitive to binding on one site on the human chorionic gonadotropin (HCG) molecule, a specific marker to pregnancy because in healthy women, HCG is synthesized exclusively by the placenta. In medicine, monoclonal antibodies are being used to stage and to localize malignant cells of cancer, and it is anticipated that they will be used in the future to combat disease such as lupus erythematosus, juvenile-onset diabetes, and myasthenia gravis.

Human gene therapy, used to prevent, treat, cure, diagnose, or mitigate human disease caused by genetic disorders, represents another promising new technology. The human body contains up to 100,000 genes. Genes that are aligned on a double strand of DNA in the nucleus of every cell control all of the body's functions. Base pairs of adenine (A) and thymine (T), and cytosine (C), and guanine (G), constitute the instructions on a gene. Only those genes necessary for a specific cell's function are active or expressed. When a gene is expressed, a specific type of protein is produced. In genetic-based diseases, gene expression may be altered and/or gene sequences may be mismatched, partly missing, or repeated too many times, causing cellular malfunction and disease.

Gene therapy is a medical intervention based on the modification of the genetic material of living cells. Cells may be modified outside the body (ex vivo) for subsequent administration, or they may be modified within the body (in vivo) by gene therapy products given directly to the patient. In either case, gene therapy involves the transfer of new genetic material to the cells of a patient afflicted with a genetic disease. The genetic material, usually cloned DNA, may be transferred into the patient's

cells physically, as through microinjection, through chemically mediated transfer procedures, or through disabled retroviral gene transfer systems that integrate genetic material directly into the host cell chromosomes (17–19)

The first human gene therapy used was to treat adenosine deaminase (ADA) deficiency, a condition that results in abnormal functioning of the immune system. Therapy consisted of the administration of genetically modified cells capable of producing ADA (18). Many emerging biopharmaceutical companies are exploring the application of gene therapy to treat sickle cell anemia, malignant melanoma, renal cell cancer, heart disease, familial hypercholesteremia, cystic fibrosis, lung and colorectal cancer, and AIDS. The first commercialized gene therapy product is expected to reach the market soon after the publication date of this textbook (20).

Although there is justified excitement and great expectation for the potential of the new biotechnologies in the development of advanced therapies, the work of the synthetic organic chemist remains today's most usual source of new drugs. The modern chemists's work is enhanced by computer-based molecular modeling, access to hugh chemical libraries, and through the use of high throughput screening in discovering compounds having an affinity for specific biological target sites (21–22).

A "Goal Drug"

In theory, a "goal drug" would produce the specifically desired effect, be administered by the most desired route (generally orally) at minimal dosage and dosing frequency, have optimal onset and duration of activity, exhibit no side effects, and following its desired effect would be eliminated from the body efficiently, completely, and without residual effect. It would also be easily produced at low cost, be pharmaceutically elegant, and physically and chemically stable under various conditions of use and storage. Although not completely attainable in practice, these qualities and features are sought in drug and dosage form design.

Methods of Drug Discovery

Although some drugs may be the result of fortuitous discovery, most drugs are the result of carefully designed research programs of screening, molecular modification, and mechanism-based drug design (23).

Random or nontargeted screening involves the testing of large numbers of synthetic organic com-

pounds or substances of natural origin for biologic activity. Random screens may be used initially to detect an unknown activity of the test compound or substance or to identify the most promising compounds to be studied by more sophisticated *nonrandom* or targeted screens to determine a specific activity.

Although random and nonrandom screening programs can examine a host of new compounds for activity, sometimes promising compounds may be overlooked if the screening models are not sensitive enough to reflect accurately the specific disease against which the agent, or its metabolites, may be useful (24).

To detect and evaluate biological activity, *bioassays* are used to differentiate the effect and potency (strength of effect) of the test agent compared with controls of known action and effect. The initial bioassays may be performed in vitro using cell cultures to test the new agent's effect against enzyme systems or tumor cells, whereas subsequent bioassays may be performed in vivo and involve more expensive and disease-specific animal models.

Newer methods, as high throughput screening, are capable of examining 15,000 chemical compounds a week using 10–20 biological assays (22). To be effective, this requires a sizeable and chemically diverse collection of compounds to examine, which many pharmaceutical and chemical companies have in "chemical libraries." Frequently these libraries, which may contain hundreds of thousands of compounds, are purchased or licensed from academic or commercial sources. With the advent of techniques as combinatorial chemistry, it has become feasible to increase substantially the size and diversity of a chemical library (22).

Molecular modification involves the chemical alteration of a known and previously characterized organic compound (frequently a *lead compound*; see next section) for the purpose of enhancing its usefulness as a drug. This could mean—enhancing its specificity for a particular body target site; increasing its potency; improving its rate and extent of absorption; modifying to advantage its time-course in the body; reducing its toxicity; or changing its physical or chemical properties (e.g., solubility) to provide pharmaceutically desired features (23). The molecular modifications may be slight or substantial, involving changes in functional groups, ring structures, or configuration. Knowledge of chemical structure-pharmacologic activity relationships (SAR) plays an important role in designing new drug molecules. Through molecular modification, new chemical entities and improved therapeutic agents result. Figures 2.3A and 2.3B present the
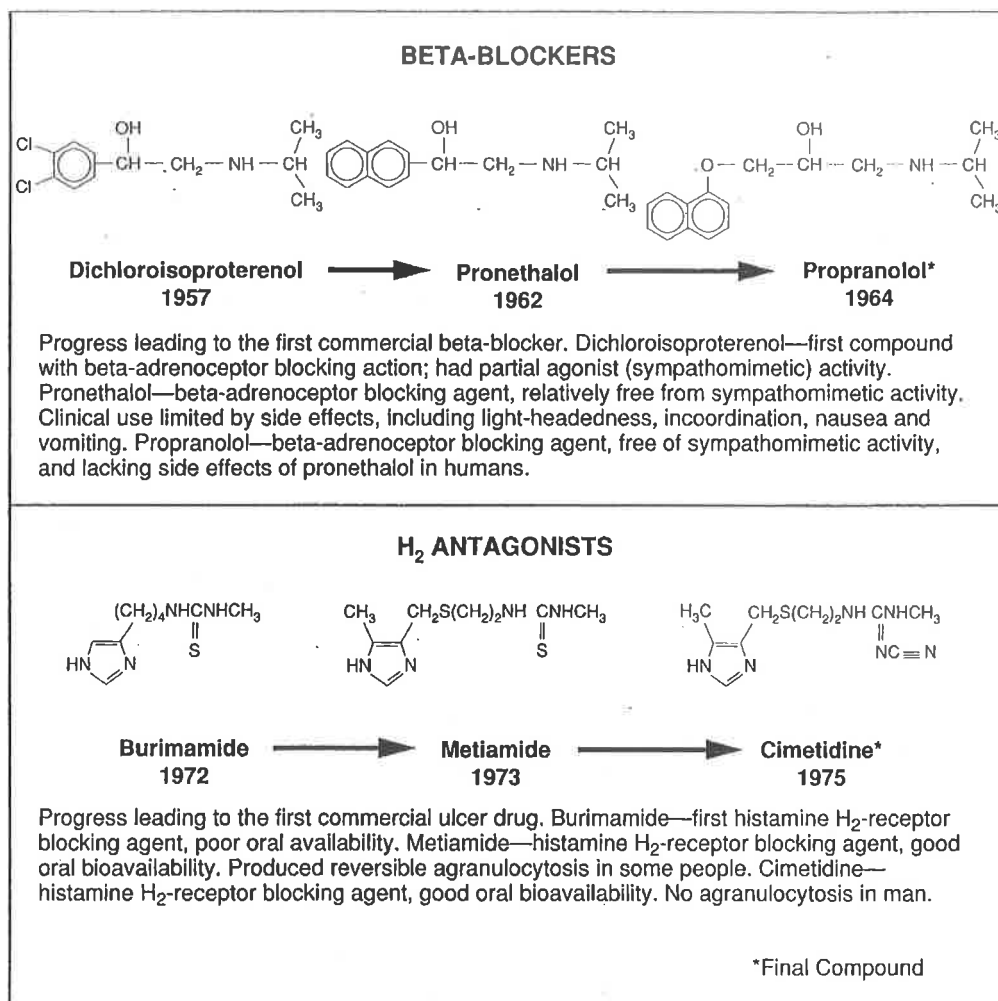
BETA-BLOCKERS

Dichloroisoproterenol → **Pronethalol** → **Propranolol***
1957　　　　　　**1962**　　　　　　**1964**

Progress leading to the first commercial beta-blocker. Dichloroisoproterenol—first compound with beta-adrenoceptor blocking action; had partial agonist (sympathomimetic) activity. Pronethalol—beta-adrenoceptor blocking agent, relatively free from sympathomimetic activity. Clinical use limited by side effects, including light-headedness, incoordination, nausea and vomiting. Propranolol—beta-adrenoceptor blocking agent, free of sympathomimetic activity, and lacking side effects of pronethalol in humans.

H_2 ANTAGONISTS

Burimamide → **Metiamide** → **Cimetidine***
1972　　　　　**1973**　　　　　**1975**

Progress leading to the first commercial ulcer drug. Burimamide—first histamine H_2-receptor blocking agent, poor oral availability. Metiamide—histamine H_2-receptor blocking agent, good oral bioavailability. Produced reversible agranulocytosis in some people. Cimetidine—histamine H_2-receptor blocking agent, good oral bioavailability. No agranulocytosis in man.

*Final Compound

Fig. 2.3 - *Molecular modifications leading to the development of the first commercial beta blocker, propranolol, and the first commercial histamine H_2-receptor blocking agent, cimetidine. (Reprinted with permission from Maxwell RA. The state of the art of the science of drug discovery. Drug Development Research 1984;4:375–389; through Pharmaceutical Research: Therapeutic and Economic Value of Incremental Improvements, 1990, p. 12. Courtesy of National Pharmaceutical Council, Reston, VA).*

molecular modifications that led to the discoveries of the first commercial beta blocker, propranolol, and the first commercial histamine H_2-receptor blocking agent, cimetidine.

Mechanism-based drug design involves molecular modification in designing a drug that interferes specifically with the known or suspected biochemical pathway or mechanism of a disease process. The intention is the interaction of the drug with specific cell receptors, enzyme systems, or the metabolic processes of pathogens or tumor cells,

resulting in a blocking, disruption, or reversal of the disease process. In designing drugs on this basis, it is essential to understand the biochemical pathway of the disease process and the manner in which it is regulated. *Molecular graphics*, the use of computer graphics to represent and manipulate the structure of the drug molecule to"fit"the simulated molecular structure of the receptor site, is a useful and complementary tool in drug molecule design.

An example of mechanism-based drug design is the compound enalaprilat (Vasotec), which inhibits

the angiotensin-converting enzyme that catalyzes the conversion of angiotensin I to the vasoconstrictor substance angiotensin II. Inhibition of the enzyme results in decreased plasma angiotensin II leading to decreased vasopressor effects and the drug's use in lowering blood pressure in treating hypertension. Another example is ranitidine (Zantac), an inhibitor of histamine at the histamine H_2-receptors including receptors on the gastric cells. This inhibits gastric acid secretion making the drug effective in the treatment of gastric ulcers and other gastrointestinal conditions related to the production of gastric acid. A third example is sertraline (Zoloft), which inhibits the central nervous system neuronal uptake of serotonin, making the drug useful in the treatment of depression.

A "Lead Compound"

A "lead compound" is a prototype chemical compound that has a fundamental desired biologic or pharmacologic activity. Although active, the lead compound may not possess all of the features desired; i.e., potency, absorbability, solubility, low toxicity, and so forth. Thus, the medicinal chemist may seek to modify the lead compound's chemical structure to achieve the desired features while reducing the undesired ones. The chemical modifications produce analogs that have additional or different functional chemical groups, altered ring structures, or different chemical configurations. The results are modified chemical compounds capable of having different interactions with the body's receptors, thereby eliciting different actions and intensities of action.

The synthesis of derivatives of the prototype chemical may ultimately lead to successive "generations" of new compounds of the same pharmacologic type. This may be exemplified by the development of new generations of cephalosporin antibiotics; additional H_2 antagonists from the pioneer drug cimetidine; and the large series of antianxiety drugs derived from the benzodiazepine structure and the innovator drug chlordiazepoxide (Librium).

Most drugs exhibit activities secondary to their primary pharmacologic action. It is not uncommon to take advantage of a secondary activity by developing new compounds, through molecular modification, that amplify the secondary use of the drug, or by gaining approval to market the drug for a secondary indication. For example, the drug finasteride (Proscar) was originally developed and approved to treat benign prostatic hyperplasia. Later, the same drug, at a lower recommended dosage, was approved (as Propecia) to treat male pattern baldness.

Prodrugs

Prodrug is a term used to describe a compound that requires metabolic biotransformation after administration to produce the desired pharmacologically active compound. The conversion of an inactive prodrug to an active compound occurs primarily through enzymatic biochemical cleavage. Depending on the specific prodrug-enzyme interaction, the biotransformation may occur anywhere along the course of drug transit or at the body site where the requisite enzymes are sufficiently present. An example of a prodrug is enalapril (enalapril maleate, Vasotec) which, after oral administration, is bioactivated by hydrolysis to enalaprilat, an ACE inhibitor used in the treatment of hypertension. Prodrugs may be designed preferentially for the following reasons (23).

Solubility

A prodrug may be designed to possess solubility advantages over the active drug, enabling the use of specifically desired dosage forms and routes of administration. For example, if an active drug is insufficiently soluble in water to prepare a desired intravenous injection, a water-soluble prodrug could be prepared through the addition of a functional group that later would be detached by the metabolic process to yield, once again, the active drug molecule.

Absorption

A drug may be made more water- or lipid-soluble, as desired, to facilitate absorption via the intended route of administration.

Biostability

If an active drug is prematurely destroyed by biochemical or enzymatic processes, the design of a prodrug may protect the drug during its transport in the body. In addition, the use of a prodrug could result in site-specific action of greater potency.

Prolonged Release

Depending on a prodrug's rate of metabolic conversion to active drug, it may provide prolonged drug release and extended therapeutic activity.

FDA's Definition of a New Drug

According to the FDA, any drug that is not recognized among experts, qualified by scientific

training and experience, as being safe and effective under the conditions recommended for its use is termed a "new drug" (1).

A drug need not be a new chemical entity to be considered a new drug by the FDA. A change in a previously approved drug product's formulation or method of manufacture constitute's "newness" under the law since such changes can alter the therapeutic efficacy and/or safety of a product.

A new combination of two or more old drugs or a change in the usual proportions of drugs in an established combination product would be considered "new" if a question of safety or efficacy is introduced by the change.

A proposed new use for an established drug, a new dosage schedule or regimen, a new route of administration, or a new dosage form all cause a drug or drug product to be "new" and reconsidered for safety and efficacy.

Drug Nomenclature

When first synthesized, or identified from a natural source, an organic compound is represented by an *empirical formula,* as $C_{14}H_{19}Cl_2NO_2$ for chlorambucil, which indicates the number and the relationship of the atoms comprising the molecule. As knowledge of the relative locations of these atoms is gained, the compound receives a *systematic chemical name,* as 4-[bis(2-chloroethyl)amino] − 4 − [p-[Bis(2-chloroethyl)amino]phenyl]butyric acid. To be adequate and fully specific, the name must reveal every part of the compound's molecular structure, so that it describes only that compound and no other. The systematic name is generally so formidable that it soon is replaced in scientific communication by a shortened name, which, although less descriptive chemically, is understood to refer only to that chemical compound. This shortened name is the chemical's *nonproprietary* (or generic) name (e.g., chlorambucil; see Fig. 1.2).

Today many companies give their new compounds *code numbers* before the assignment of a nonproprietary name. These code numbers take the form of an identifying prefix letter or letters that identify the drug's sponsor, followed by a number that further identifies the test compound (for example, SQ 14,225, the investigational code number for the drug captopril, initially developed by Squibb). The code number frequently stays with a compound from its initial preclinical laboratory investigation through human clinical trials.

When the results of testing indicate that a compound shows sufficient promise of becoming a drug, the sponsor may formally propose a nonproprietary name and may also apply to the U.S. Patent Office (and foreign agencies as well) for a proprietary or trademark name. Should the drug receive recognition in an official compendium, the nonproprietary name established during the period of the drug's early usage is adopted. Nonproprietary names are issued only for single agents whereas proprietary or trademark names may be associated with a single chemical entity or with a mixture of chemicals comprising a specific proprietary product.

The task of designating appropriate nonproprietary names for chemical agents rests primarily with the United States Adopted Names Council (USAN Council). This organized effort at coining nonproprietary names for drugs was inaugurated in 1961 as a joint project of the American Medical Association and the United States Pharmacopeial Convention. They were joined in 1964 by the American Pharmaceutical Association to form the USAN Council; in 1967, the Food and Drug Administration was invited to take part in the work of the Council.

The United States Pharmacopeial Convention publishes the USAN and the *USP Dictionary of Drug Names.* In addition to listing the US Adopted Names, the reference also includes brand names of research-oriented firms, investigational drug code designations, official names of USP and NF articles with their chemical names and graphic formulas, and international nonproprietary names (INN) published by the World Health Organization (WHO). This reference of drug names now includes more than 18,000 entries.

A proposal for a USAN usually originates from a firm or an individual who has developed a substance of potential therapeutic usefulness to the point where there is a distinct possibility of its being marketed in the United States. Occasionally, the initiative is taken by the USAN Council in the form of a request to parties interested in a substance for which a nonproprietary name appears to be lacking. Proposals are expected to conform to the Council's guidelines for coining nonproprietary names. The name should: 1) be short and distinctive in sound and spelling and not be such that it is easily confused with existing names, 2) indicate the general pharmacologic or therapeutic class into which the substance falls or the general chemical nature of the substance if the latter is associated with the specific pharmacologic activity, and 3) embody the syllable or syllables characteristic of a related group of compounds.

When general agreement on a name has been reached between the Council and the drug's sponsor, it is announced as a "Proposed USAN." This indicates the Council's intention to adopt the name and serves notice on those who wish to protest the selection. The tentatively adopted USAN is then submitted for consideration by various American and foreign drug regulatory agencies, including the World Health Organization, the British Pharmacopoeia Commission, the French Codex, the Nordic Pharmacopeia, the United States Pharmacopeia and National Formulary, and the U.S. Food and Drug Administration. Under the 1962 Drug Amendments, the Secretary of the Department of Health and Human Services has authority to designate the nonproprietary name for any drug in the interest of usefulness or simplicity. The authority is delegated to the Commissioner of the Food and Drug Administration within the Department. If no objections are raised, adoption is considered final, and the USAN is published in the various literature of the medical and pharmaceutical professions. On rare occasion, a USAN-adopted name is changed to foster clarity or uniformity. With the creation of the USAN Council and the cooperation of the interested parties on a worldwide basis, nonproprietary drug nomenclature has become standardized.

Biological Characterization

Prospective drug substances must undergo preclinical testing for biologic activity to assess their potential as useful therapeutic agents. These studies fall into the general areas of pharmacology, drug metabolism, and toxicology, and involve many types of scientists including general biologists, microbiologists, molecular biologists, biochemists, geneticists, pharmacologists, physiologists, pharmacokineticists, pathologists, toxicologists, statisticians, and others. Their work leads to the determination of whether a chemical agent possesses adequate features of safety and sufficient promise of usefulness to pursue as a prospective new drug.

To judge whether a drug is safe and effective, information must be gained on how it is absorbed, distributed throughout the body, stored, metabolized, excreted, and how it affects the action of the body's cells, tissues, and organs. Scientists have developed studies that may be conducted outside the living body by using cell and tissue culture and computer programs that simulate human and animal systems. Cell cultures are being used increasingly to screen for toxicity before progressing to whole-animal testing. Computer models help to predict the properties of substances and their probable actions in living systems. Although these non-animal systems have reduced dependence on the use of animals in drug studies, they have not completely replaced the need to study drugs in whole animals as a safeguard before their administration to humans.

Pharmacology

Within its broad definition, *pharmacology* embraces the physical and chemical properties, biochemical and physiological effects, mechanisms of action, absorption, distribution, biotransformation, excretion, and useful applications of drugs (25). From this basic field of study come such subareas as *pharmacodynamics*, which is the study of the biochemical and physiological effects of drugs and their mechanisms of action; *pharmacokinetics*, which deals with the absorption, distribution, metabolism or biotransformation, and excretion (ADME) of drugs; and *clinical pharmacology*, which applies pharmacologic principles to the study of the effects and actions of drugs in humans.

Today's emphasis in the development of new drugs is directed toward identifying the cause and process of a disease and then designing drug molecules capable of interfering with that process. Although the precise cause of each disease is not yet known, what is known is that most diseases arise from a biochemical imbalance, an abnormal proliferation of cells, an endogenous deficiency, or an exogenous chemical toxin or invasive pathogen.

The biochemical processes within the body's cells involve intricate enzymatic reactions. An understanding of the role of a particular enzyme system in the body's healthy state and disease state can lead to the design of drugs that affect the enzyme system with positive results, as exemplified earlier in this chapter for the drug enalaprilat (Vasotec).

Different drug substances produce different effects on the biological system due to the specific interactions between a drug's chemical structure and specific cells or cellular components of a particular tissue or organ, termed receptor sites (Fig. 2.4). The action of most drugs takes place at the molecular level with the drug molecules interacting with the molecules of the cell structure or its contents. The selectivity and specificity of drugs for a certain body tissue—for example, drugs that act primarily on the nerves, heart, or kidney—are related to specific sites on or within the cells, receptive only to chemicals of a particular chemical structure and configuration. This is the basis for *structure–activity*
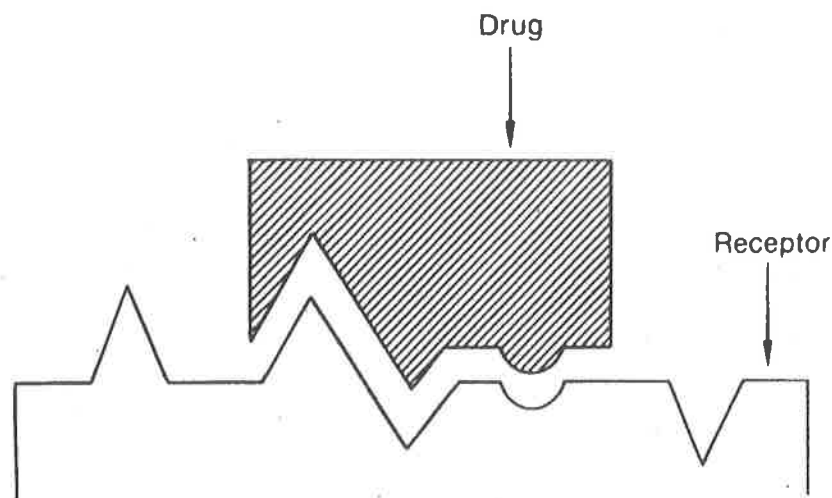
Fig. 2.4   *Schematic drawing of receptor site and substrate (drug). (Reprinted with permission from Clark FH, ed. How Modern Medicines are Discovered. Courtesy of Futura Publishing Company, Inc.)*

relationships (SAR) established for drugs and for families of drugs within therapeutic categories. Studies of the pharmacologic activities of a series of analogs with varied functional groups and side chains can reveal the most specific structure for a given drug–cell or drug–enzyme interaction.

Although receptors for many drugs have yet to be identified, they, like the active centers of enzymes, are considered to be carboxyl, amino, sulfhydryl, phosphate, and similar reactive groups oriented on or in the cell in a pattern complementary to that of the drugs with which they react. The binding of a drug to the receptor is thought to be accomplished mainly by ionic, covalent, and other relatively weak reversible bonds. Occasionally, firm covalent bonding is involved, and the drug effect is then slowly reversible.

There is a relationship between the *quantity* of drug molecules available for interaction and the capacity of the specific receptor site. For instance, after a dose of drug and its transit to the site of action, the cell's receptors may or may not become fully saturated with interacting drug. When the receptors *are* saturated, the effects of the specific interaction are maximized. Any additional drug present (as in the circulation) and not participating in the interaction may serve as a reservoir to replace drug molecules that become released from the complex. Two drugs, when present in a biologic system, may compete for the same binding sites, with the drug having the stronger bonding attraction for the site

generally prevailing. Already-bound molecules of the more weakly bound drug may be replaced from the binding site and left free in the circulation as unbound drug.

Certain cells within the body are capable of binding drugs without eliciting a drug effect. These cells act as carriers and may be important to a drug's transport to active sites or to sites of the drug's biotransformation and elimination.

The process of evaluating chemical compounds for biologic activity and the determination of their mechanisms of action is the responsibility of the pharmacologist. In vitro cultures of cells and enzymes systems, and in vivo animal models are used to define a chemical's *pharmacologic profile*.

To define a pharmacologic profile, pharmacologists progress stepwise through increasingly sophisticated levels of evaluation, based on the test compound's success in prior studies. Whole-animal studies are reserved for test compounds that have demonstrated reasonable potential as a drug candidate.

Among the early studies undertaken are the determination of a compound's selectivity for various receptors and its activity against select enzyme systems. Studies of the compound's effects on cell function are then performed to detect evidence of efficacy and to determine whether the compound is an agonist or antagonist. These are followed by studies with isolated animal tissues to define further the compound's activity and selectivity. Then

whole-animal studies are used to evaluate the pharmacologic effects of the agent on specific organ systems. Finally, studies are undertaken using animal models of human disease for which the compound is considered a drug candidate.

The majority of animal testing is done using small animals, usually rodents (mouse, rat) for a number of reasons including cost, availability, the small amount of drug required for a study, the ease of administration by various routes (oral, inhalation, intravenous), and experience with drug testing in these species. However, in final pharmacologic and toxicologic studies, two or more animal species are used as required by the FDA, including a rodent and a nonrodent. Drugs are studied at various dose levels to determine effect, potency, and toxicity.

The primary objective of the animal studies is to obtain basic information on the drug's effects that may be used to predict safe and effective use in humans. This is a difficult task because of species variation and the fact that animals are not absolute predictors of human response. However, a number of animal models have been developed to mimic certain human diseases, and these are used effectively. For instance, there are animal models for type I diabetes and hypertension, using genetically diabetic and hypertensive animals, respectively, and for tumor growth, using tumor transplants into various species. Certain animal species have been determined to be best for certain studies of organ systems, or as human disease models, including: the dog and rat for hypertension; the dog and guinea pig for respiratory effects; the dog for diuretic activity; the rabbit for blood coagulation; and the mouse and rat for central nervous system studies (26–27). Unfortunately, useful animal models are not available for every human disease. As a drug candidate progresses in its preclinical pharmacologic evaluation, drug metabolism and toxicity tests are initiated.

Drug Metabolism

A series of animal studies of a proposed drug's absorption, distribution, metabolism, and elimination (ADME) are undertaken to determine: 1) the *extent* and *rate* of drug absorption from various routes of administration, including the one intended for human use; 2) the rate of distribution of the drug through the body, and the site(s) and duration of the drug's residence; 3) the rate, primary and secondary sites, and mechanism of the drug's metabolism in the body, and the chemistry and

pharmacology of any metabolites; and 4) the proportion of administered dose eliminated from the body, and its rate and route of elimination. In these studies, a minimum of two animal species are employed (generally the same as used in the pharmacologic and toxicologic studies), a rodent and a nonrodent, usually a dog.

The biochemical transformation or metabolism of drug substances is the body's means of transforming nonpolar drug molecules into polar compounds, which are more readily eliminated. Specific and nonspecific enzymes participate in drug metabolism, primarily in the liver, but also in the kidneys, lung, and gastrointestinal tract. Drugs that enter the hepatic circulation after absorption from the gut, as after oral administration, are particularly exposed to rapid drug metabolism. This transit through the liver and exposure to the hepatic enzyme system is termed the *first-pass effect*. If the first-pass effect is to be avoided, other routes of administration (buccal, rectal) may be used that allow the drug to be absorbed into the systemic circulation through blood vessels other than hepatic.

Drug metabolism or biotransformation frequently results in the production of one or more metabolites of the administered drug, some of which may be pharmacologically active compounds, others not. As noted previously, drug metabolism may be essential to convert prodrugs to active compounds. For reasons of drug safety, it is important to determine whether a drug's metabolic products are toxic or nontoxic to the animal, and later, to the human. When metabolites are found, they are chemically and biologically characterized for activity and toxicity. Some new drugs have been discovered as metabolic byproducts or metabolites of parent compounds.

ADME studies are performed through the timely collection and analysis of urine, blood, and feces samples, and through a careful examination of animal tissues and organs upon autopsy. In addition, special studies are undertaken to determine: the presence, if any, of a test drug or its metabolites in the milk of lactating animals; the ability of the drug to cross the placental barrier and enter the fetal blood supply; and, the long-term retention of drug or metabolites in the body. In studying the formation and disposition of metabolites, a radioactive label is commonly incorporated into the administered compound and traced in the animal's waste products and tissues.

The relationship between ADME and drug product development is discussed in Chapter 4.

Toxicology

Toxicology is the area of pharmacology that deals with the adverse, or undesired, effects of drugs (25). Although the ability to predict the safe use of a new drug in humans based on preclinical animal studies is desirable, it is not entirely achievable. The direct extrapolation of preclinical animal safety data to humans is difficult because of species variation, different dose—response relationships, immunologic differences, subjective reactions nondeducible in animals (such as headache), and for other reasons (27). Although many adverse reactions that occur in humans cannot be predicted in advance through animal studies, the greater the number of animal species tested which demonstrate a toxic effect, the greater the likelihood the effect will also be seen in humans.

In drug development programs, preclinical drug safety evaluation (DSE) or toxicity studies are undertaken to determine: 1) the substance's potential for toxicity with short-term (acute effects) or long-term use (chronic effects); 2) the substance's potential for specific organ toxicity; 3) the mode, site, and degree of toxicity; 4) dose—response relationships, for low- high- and intermediate doses over a specified time course; (5) gender, reproductive, or teratogenic toxicities; and 6) the substance's carcinogenic and genotoxic potential.

Initial toxicology studies are conducted on rodents. After successful initial testing, a nonrodent species, usually a dog, is added to the testing program to develop the FDA-required two species toxicology profile. The toxicology profile includes acute or short-term toxicity; subacute or subchronic toxicity; chronic toxicity; carcinogenicity testing; reproduction studies; and mutagenicity screening (9, 28–29). Figure 2.1 shows that short-term and long-term toxicity studies span the entire program of drug development, from preclinical studies through clinical trials and into postmarketing surveillance.

Acute or Short-Term Toxicity Studies

These studies are designed to determine the toxic effects of a test compound when administered in a single dose and/or in multiple doses over a short period, usually a single day. Although various routes of administration may be used (such as lavage dosing via gastric tube), the studies should be conducted to represent the intended route for human use.

The test compound is administered at various dose levels, with toxic signs observed for onset, progression or reversal, severity, mortality, and rates of incidence. Doses are ranged, to find the largest single dose of the test compound that will not produce a toxic effect; the dose level at which severe toxicity occurs; and intermediate toxicity levels. The animals are observed and compared with controls for eating and drinking habits, weight change, toxic effects, psychomotor changes, and any other signs of untoward effects, usually over a 30-day postdose period. Feces and urine specimens are collected and clinical laboratory tests performed to detect changes in clinical chemistry and other changes that could indicate toxicity. When they occur, animal deaths are recorded, studied by histology and pathology, and statistically evaluated on the basis of dose—response, gender, age, intraspecies, interspecies, and against laboratory controls.

Subacute or Subchronic Studies

In designing an animal toxicology program, relationships to projected human clinical studies for safety must be considered. For example, animal toxicity studies of a minimum of 2 weeks duration of daily drug administration at three or more dosage levels to two animal species are required to support the initial administration of a single dose in human clinical testing (8). These studies are termed *subacute* or *subchronic*. The initial human dose is usually one-tenth of the highest nontoxic dose (based on a milligram-per-kilogram weight basis) shown during the animal studies. For drugs intended to be given to humans for a week or more, animal studies of 90 to 180 days in length must demonstrate safety. These are termed *chronic toxicity* studies. And, if the drug is to be used for a chronic human illness, long-term animal studies of 1 year or longer must be undertaken to support human use. Some animal toxicity studies last 2 years or longer and may be used to corroborate findings obtained during the course of human clinical trials.

Included in the subchronic and chronic studies are comparative data of test and control animal species, strain, sex, age, dose levels and ranges, routes of administration, duration of treatment, observed effects, mortality, body weight changes, food/water consumption, physical examinations (e.g., ECG, ophthalmic), hematology, clinical chemistry, organ weights, gross pathology, neoplastic pathology, histopathology, urinalysis, ADME data, and other (28). Figure 2.5 shows a toxicologist examining research data of body weight changes during preclinical rodent studies.

Carcinogenicity Studies

Carcinogenicity testing is usually a component of chronic testing and is undertaken when the compound has shown sufficient promise as a drug to enter human clinical trials. Carcinogenicity stud-
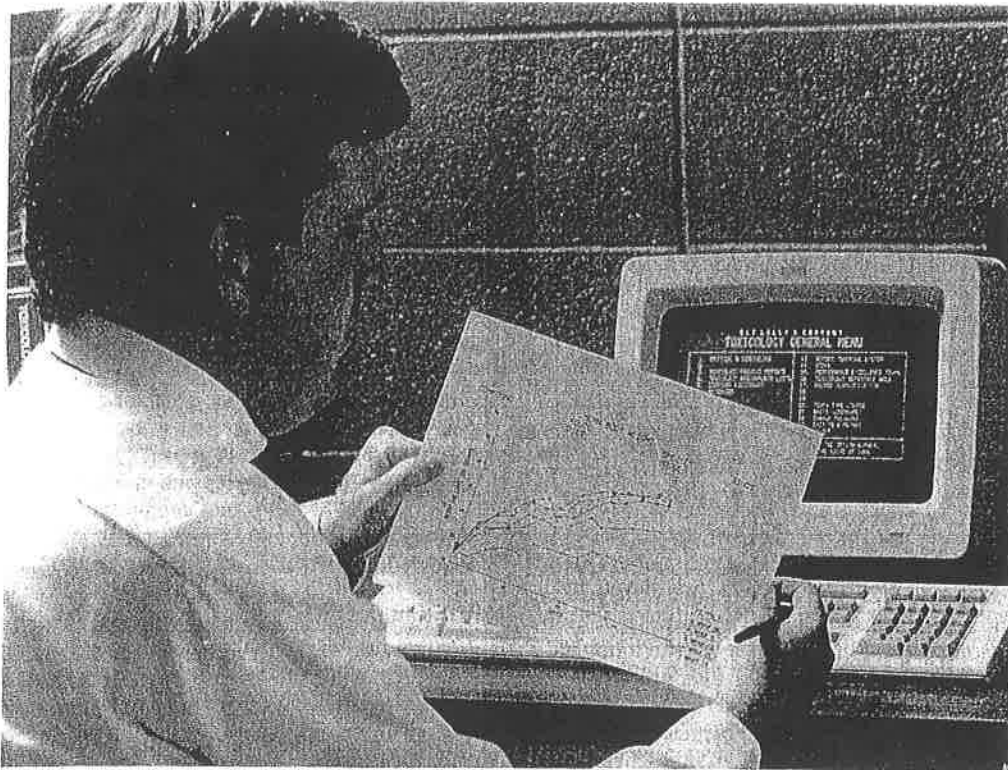
Fig. 2.5 *A toxicologist examining research data of body weight changes during preclinical studies in mice. (Courtesy of Toxicology Research Laboratories, Lilly Research Laboratories, Division of Eli Lilly and Co.)*

ies are usually carried out in a limited number of rat and mouse strains for which there is reasonable information on spontaneous tumor incidence.

Dose-ranging studies are done with female and male animals using high, intermediate, and low doses over a 90-day period. For carcinogenicity studies, the high dose should be only high enough (the maximum tolerated dose) to elicit signs of minimal toxicity without significantly altering the animal's normal lifespan due to effects other than carcinogenicity (30).

Carcinogenicity studies are long term (18–24 months), with surviving animals sacrificed and studied at defined weeks during the test period. Data are collected and evaluated on the causes of animal death (other than sacrifice), tumor incidence, type and site, and necropsy findings. The occurrence of preneoplastic lesions and/or tissue-specific proliferative effects are important findings.

Reproduction Studies

These studies are undertaken to reveal *any* effect of an active ingredient on mammalian reproduc-

tion. Included in these studies are fertility and mating behavior, early embryonic and pre- and post-natal development, multigenerational effects, and teratology. The combination of studies allows exposure from conception to sexual maturity and allows immediate and latent effects to be detected through complete life cycles and through successive generations.

In these studies, the maternal parent, fetus, neonates, and weaning offspring are evaluated for anatomical abnormalities, growth, and development. The same species of animal used in other toxicity studies are used in reproductive studies, usually the rat. In *embryotoxicity* studies only, a second mammalian species traditionally has been required. The rabbit is the preferred choice due to practicality and the extensive background knowledge accumulated on this species.

In reproductive studies, as is the case for other toxicity studies, the doses selected and the routes of administration used are critical. A high-dose, based on previous acute and chronic toxicity and pharmacokinetic studies, is selected with lower dosages

chosen in descending sequence. Setting close dosage intervals is useful to reveal trends in dose-related toxicity. Although once daily dosing is usual, the drug's pharmacokinetics may influence the frequency of dosing (31). The route or routes of administration used should be similar to that intended for human use. A single route of administration may be acceptable if it can be shown that a similar drug distribution (kinetic profile) results from different routes of administration.

Genotoxicity or Mutagenicity Studies

These studies are performed to determine if the test compound can affect gene mutation, or cause chromosome or DNA damage. Strains of *Salmonella typhimurium* are routinely used in assays to detect mutations (9,32).

Early Formulation Studies

As a promising compound is characterized for biological activity, it is also evaluated with regard to those chemical and physical properties that have a bearing on its ultimate and successful formulation into a stable and effective pharmaceutical product. This is the area of responsibility of pharmaceutical scientists and formulation pharmacists trained in the field of *pharmaceutics*. When sufficient information is gleaned on the compound's physical and chemical properties, initial formulations of the dosage form are developed for use in human clinical trials. During the course of the clinical trials, the proposed product is developed further, from initial formulation to final formulation, and from pilot plant (or small-scale production) to scale-up, in preparation for large-scale manufacturing.

To provide sufficient quantities of the bulk chemical (drug) compound for the sequence of preclinical studies, clinical trials, and small-scale and large-scale dosage form production, the careful planning, scheduling, and implementation of the bulk chemical's production must be undertaken by chemical engineers. Quality control and validation must be built into each step of the process.

Full documentation of the chemistry, manufacturing, and controls (CMC) is an essential part of all drug applications filed with the FDA (1, 33).

Preformulation Studies

Each drug substance has intrinsic chemical and physical characteristics that must be considered before the development of a pharmaceutical formulation. Among these are the drug's solubility, parti-

tion coefficient, dissolution rate, physical form, and stability. These and other factors are considered more fully in Chapter 3 and throughout the text, but are briefly noted here as an introduction to their importance in the preparation of dosage forms for drug evaluation in human clinical trials, and, in the development of a final product submitted to the FDA for marketing approval.

Drug Solubility

A drug substance administered by any route must possess some aqueous solubility for systemic absorption and therapeutic response. Poorly soluble compounds (e.g., less than 10 mg/mL aqueous solubility) may exhibit either incomplete or erratic absorption and thus produce a minimal response at desired dosage. Enhanced aqueous solubility may be achieved through the preparation of more soluble derivatives of the parent compound, such as salts or esters, through chemical complexation, or through drug particle-size reduction.

Partition Coefficient

To produce a pharmacologic response, a drug molecule must first cross a biologic membrane of protein and lipid, which acts as a lipophilic barrier to many drugs. The ability of a drug molecule to penetrate this barrier is based, in part, on its preference for lipids (lipophilic) versus its preference for an aqueous phase (hydrophilic). A drug's partition coefficient is a measure of its distribution in a lipophilic/hydrophilic phase system, and is indicative of its ability to penetrate biologic multiphase systems.

Dissolution Rate

The speed, or rate, at which a drug substance dissolves in a medium is called its *dissolution rate.* Dissolution rate data, when considered along with data on a drug's solubility, dissolution constant, and partition coefficient, can provide an indication of the drug's absorption potential following administration. For a chemical entity, its acid, base, or salt forms, as well as its physical form (e.g., particle size), may result in substantial differences in the dissolution rate.

Physical Form

The crystal or amorphous forms and/or the particle size of a powdered drug can affect the dissolution rate, and thus the rate and extent of absorption, for a number of drugs. For example, by increasing powder fineness and therefore the surface area of a poorly soluble drug, its dissolution

rate in the gut is enhanced (through greater drug/gastrointestinal fluid exposure) and its biologic absorption increased. Small and controlled particle size is also critical for drugs administered to the lung by inhalation. The smaller the particle, the deeper is the penetration into the alveoli. Thus, by selective control of the physical parameters of a drug, biologic response may be optimized.

Stability

The chemical and physical stability of a drug substance alone, and when combined with formulation components, is critical in preparing a successful pharmaceutical product. For a given drug, one type of crystal structure may provide greater stability than other structures and may therefore be preferred. For drugs susceptible to oxidative decomposition, the addition of antioxidant stabilizing agents to the formulation may be required to protect potency. For drugs destroyed by hydrolysis, protection against moisture in formulation, processing, and packaging may be required to prevent decomposition. In every case, drug stability testing at various temperatures, conditions of relative humidity (RH)—as 40°C 75% RH/30°C 60% RH—durations, and environments of light, air, and packaging is essential in assessing drug and drug product stability. Such information is vital in developing label instructions for use and storage, assigning product expiration dating, and packaging and shipping.

Initial Product Formulation and Clinical Trial Materials (CTM)

An initial product is formulated using the information gained during the preformulation studies and with consideration of the dose(s), dosage form, and route of administration desired for the clinical studies and for the proposed marketed product. Thus, depending upon the design of the clinical protocol and desired final product, formulation pharmacists are called upon to develop a specific dosage form (e.g., capsule, suppository, solution) of one or more dosage strengths for administration by the intended route of administration (e.g., oral, rectal, intravenous). Additional dosage forms for other than the initial route of administration may later be developed, depending on patient requirements, therapeutic utility, and marketing assessments.

The initial formulations prepared for Phase 1 and Phase 2 of the clinical trials, although not as sophisticated and elegant as the final formulation, should be of high pharmaceutical quality, meet analytical specifications for composition, manufactur-

ing, and control, and be sufficiently stable for the period of use.

Often during Phase 1 studies, for orally administered drugs, capsules are employed containing the active ingredient alone, without pharmaceutical excipients. Excipients are included in the formulation for Phase 2 trials. During the course of the human trials, studies of the drug's absorption, distribution, metabolism, and excretion are undertaken to obtain a profile of the drug's human pharmacokinetics and biologic availability from the formulation administered. Different formulations may be prepared and examined to develop the one having the desired characteristics (see Chapter 4). During Phase 2, the final dosage form is selected and developed for Phase 3 trials and represents the formulation that is submitted to the FDA for marketing approval.

Clinical supplies or clinical trial materials (CTM), refer to all dosage formulations used in the clinical evaluation of a new drug. This includes the proposed new drug, *placebos* (nonmedicated forms for controlled studies) and drug products against which the new drug is to be compared (*comparator* drugs or drug products). They all must be prepared in indistinguishable dosage forms (look alike, taste alike, etc.) and packaged with coded labels to reduce possible bias when *blinded* studies are called for in the clinical protocol. Blinded studies are controlled studies in which at least one of the parties (e.g., patient, physician) is not knowledgeable of which product is being administered. At the conclusion of the clinical study, the codes for the products administered are broken and the clinical results statistically evaluated. Some studies are *open label* in which all parties may be aware of the products administered.

Some pharmaceutical companies have special units for the preparation, analytical control, coding, packaging, labeling, shipping, and record maintenance of clinical supplies. Other companies integrate this activity within their existing drug product development and production operations. Still other companies employ contract firms specializing in this field to prepare and manage their clinical trial materials program.

In all clinical study programs, the package label of the investigational drug must bear the statement "Caution: New Drug—Limited by Federal (or United States) Law to Investigational Use." Once received by the investigator, the clinical supplies may be administered only to subjects included in the study. Blister packaging is commonly used in clinical studies, with immediate labels containing

the clinical study or protocol number, patient identification number, sponsor number, directions for use, code number to distinguish between investigational drug, placebo, and/or comparator product, and other relevant information. Records of the disposition of the drug must be maintained by patient number, dates, and quantities administered. When there is a department of pharmacy at the site of the clinical study (e.g., university teaching hospital) pharmacists frequently assist in the control and management of clinical supplies. When an investigation is terminated, suspended, discontinued, or completed, all unused clinical supplies must be returned to the sponsor and an accounting made of used and unused product.

All formulations, from those developed initially through the final marketed version, must be prepared under the conditions and procedures set out by the FDA in its Current Good Manufacturing Practice (CGMP) guidelines (34), as outlined in Chapter 5.

The Investigational New Drug (IND) Application

Under the Food, Drug, and Cosmetic Act as amended, the sponsor of a new drug is required to file with the FDA an *Investigational New Drug Application (IND)* before the drug may be given to human subjects (1). This is to protect the rights and safety of the subjects and to ensure that the investigational plan is sound and is designed to achieve the stated objectives. The *sponsor* of an IND takes responsibility for and initiates a clinical investigation. The sponsor may be an individual (a sponsor-investigator), a pharmaceutical company, governmental agency, academic institution, or other private or public organization. The sponsor may actually conduct the study or employ, designate, or contract other qualified persons to do so. Nowadays there are many *contract research organizations* (CROs) that conduct all or designated portions of clinical studies or clinical drug trials for others through contractual arrangements.

After submission of the IND, the sponsor must delay use of the drug in human subjects for not less than 30 days from the date the FDA acknowledges receipt of the application. An IND automatically goes into effect following this period unless the FDA notifies the sponsor that, based on its review of the submission, the period is waived (and the sponsor may initiate the study early), or the investigation is being placed on a *clinical hold.*

A *clinical hold* is an order issued by the FDA to delay the start of a clinical investigation or, in the case of an ongoing investigation, to suspend the study. During a clinical hold, the investigational drug may not be administered to human subjects (unless specifically permitted by the FDA for individual patients in an ongoing study). A clinical hold is issued when there is concern that human subjects will be exposed to unreasonable and significant risk of illness or injury; where there is question over the qualifying credentials of the clinical investigators; or in instances in which the IND is considered incomplete, inaccurate, or misleading. If the concerns raised are addressed to the FDA's satisfaction, a clinical hold may be lifted and clinical investigations resumed; if not, an IND may be maintained in a clinical hold position, declared inactive, withdrawn by the sponsor, or terminated by the FDA.

Content of the IND

The content of an IND is prescribed in the *Code of Federal Regulations* and is submitted under a cover sheet (*Form FDA-1571*) (1).

Among the items required are:

- Name and address and telephone number of the sponsor of the drug;
- Name and title of the person responsible for monitoring the conduct and progress of the investigation;
- Name(s) and title(s) of the person(s) responsible for the review and evaluation of information relevant to the safety of the drug;
- Name and address of any contract research organization involved in the study;
- Identification of the phase or phases of the clinical investigation to be conducted;
- Introductory statement and general investigational plan, including: the name of the drug and all active ingredients, the drug's structural formula and pharmacological class, the formulation of the dosage form and route of administration, the broad objectives and planned duration of the study;
- Description of the investigational plan, including: the rationale for the drug/research study, the indication(s) to be studied, the approach in evaluating the drug, the types of studies to be conducted, the estimated number of subjects to be given the drug, and any serious risks anticipated based on animal studies or other human experiences with the drug;
- Brief summary of previous human experience

with the drug (domestic or foreign), including reasons if the drug has been withdrawn from any other investigation and/or marketing;

- Chemistry, manufacturing and control information, including: a complete description of the drug substance including its physical, chemical, and biological characteristics, its method of preparation, and analytical methods to assure its identity, strength, quality, purity and stability, a quantitative list of the active and inactive components of the dosage form to be administered, the methods, facilities, and controls employed in the manufacture, processing, packaging and labeling of the new drug to assure appropriate qualitative and quantitative standards and product stability during the clinical investigation;
- Pharmacology and toxicology information, including: the drug's mechanism of action (if known), information on the drug's absorption, distribution, metabolism, and excretion, and acute, subacute, chronic and reproductive and developmental toxicity studies;
- If the new drug is a combination of previously investigated components, a complete preclinical and clinical summary of these components when administered singly and any data or expectations relating to the effect when combined;
- *Clinical protocol* for each planned study (discussed in the next section);
- Commitment that an *Institutional Review Board* *(IRB)* has approved the clinical study and will continue to review and monitor the investigation (discussed in the next section);
- *Investigator Brochure* (discussed in the next section); and,
- Commitment not to begin clinical investigations until the IND is in effect, the signature of the sponsor or authorized representative, and the date of the signed application.

The Clinical Protocol

As a part of the IND application, a *clinical protocol* must be submitted to ensure the appropriate design and conduct of the investigation. Clinical protocols include:

- Statement of the purpose and objectives of the study;
- Outline of the investigational plan and study design, including the kind of control group and methods to minimize bias on the part of the subjects, investigators, and analysts;

- Estimate of the number of patients to be involved;
- Basis for subject selection, including inclusion and exclusion criteria;
- Description of the dosing plan, including dose levels, route of administration, and duration of patient exposure;
- Description of the patient observations, measurements, and tests to be used;
- Clinical procedures, laboratory tests and monitoring to be used in minimizing patient risk;
- Names, addresses and credentials of the principal investigators and subinvestigators;
- Locations and descriptions of the clinical research facilities to be used; and,
- Approval of the authorized Institutional Review Board.

Once an IND is in effect, a sponsor must submit an amendment for approval of any proposed changes. This may involve changes of dosing levels, testing procedures, the addition of new investigators, additional sites for the study, and so on.

For many years, women and the elderly were included only rarely in clinical drug investigations. Women of child-bearing age were excluded from early drug tests out of fear that the subject would become pregnant during the investigation with possible harm to the fetus. Exceptions were made only in cases of potentially life-saving drugs. However, in recognition that the general exclusion of women from drug investigations results in inadequate data on any gender-based differences in a drug's effects, the FDA now calls for the inclusion of women in numbers adequate to allow detection of clinically significant differences in drug response.

The FDA "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs" issued in 1993 states the agency's gender inclusion policy (35). Although the guideline does not require participation of women in any particular trial, it sets forth FDA's general expectations regarding the inclusion of both women and men in drug development, analysis of clinical data by gender, and assessment of potential pharmacokinetic differences between genders. In 1994, the National Institutes of Health (NIH) similarly issued its policy that women (and minorities) be included in all NIH-supported biomedical and behavioral research projects involving human subjects "unless there is a clear and compelling rationale and justification that their inclusion is inappropriate with respect to the health of the subjects or the purpose of the research" (36).

Pregnancy is a concern in drug investigations because drugs are readily transported from the maternal to the fetal circulation (37). Because of undeveloped drug detoxication and excretion mechanisms in the fetus, concentrations of drugs may actually reach a higher level in the fetus than in the maternal circulation with toxic levels resulting. To reduce the risk of fetal exposure to investigational drugs in child-bearing age women, the FDA guideline calls for pregnancy testing, use of contraception, and full information disclosure of potential fetal risks to prospective study subjects. The FDA has made a special effort to ensure that women who have a life-threatening disease (e.g., AIDS-related) are not *automatically* excluded from investigational trials of drug products for that disease due to a perceived risk of reproductive or developmental toxicity from use of the investigational drug (38). There are other instances in which drug studies/use during pregnancy are justified, as for example, agents intended to prevent Rh immunization and subsequent hemolytic disease of the newborn (39).

When a proposed drug is likely to have significant use in the elderly, elderly patients are required to be included in clinical studies to yield age-related data of a drug's effectiveness and the occurrence of adverse effects. Older people handle a drug differently, not because of age itself, but because of altered body functions such as diminished liver and kidney function, reduced circulation, and changes in drug absorption, distribution, metabolism, and excretion. Further, compared with younger adults, the elderly have a greater incidence of chronic illness and multiple disease states, and as a result, take multiple medications daily increasing the potential for drug–drug interactions. This potential is studied and defined.

Recognition of the need to examine in children new drugs intended for the pediatric patient has a similar requirement to ensure a drug's safe and effective use in this patient population. Also, differentiation in a drug's activity in minority groups and their subpopulations is important in the full assessment of a drug's potential. It is well known that there are interethnic variations both in disease incidence and in biologic response to some medications and these factors need to be considered in the clinical evaluation of drug substances. (40)

Each IND submission must have the prior approval of the *Institutional Review Board* (IRB) having jurisdiction over the site of the proposed clinical investigation. An IRB is a body of professional and public members that has the responsibility for reviewing and approving any study involving human subjects within the institution they serve. The purpose of the IRB is to protect the safety of human subjects by assessing a proposed clinical protocol, evaluating the benefits against potential risks, and ensuring that the plan includes all needed measures for subject protection. By law, the IRB shall be constituted to include persons competent to review clinical research proposals and be diverse in membership with consideration of race, gender, cultural background, and sensitivity to issues affecting the subjects and the community (41). Any substantive change or an amendment to an originally approved clinical protocol must be submitted, reviewed and approved by the IRB and the FDA before implementation.

Each clinical investigator must receive from the sponsor an *Investigator's Brochure*, which contains all of the pertinent information developed during the preclinical studies, including summary information on the drug's chemistry, pharmacology, toxicology, pharmacokinetics; formulation of the clinical trial materials; any known information related to the drug's safety and effectiveness; a description of possible risks and side effects that may be anticipated and special monitoring required; the clinical protocol and study design; criteria for patient inclusion and exclusion; laboratory and clinical tests to be performed; and drug control and record keeping information.

Each study has defined criteria for *subject inclusion or exclusion.* These criteria may relate to age, sex (as qualified above), smoking, health status, and other factors deemed necessary in a given phase of investigation. Each subject in a clinical investigation must participate willingly and with full knowledge of the benefits and risks associated with the investigation.

The sponsor of the study must certify that each person who will receive the investigational drug has given *informed consent*—that is, has been informed of the following: participation in the study is voluntary; the purpose and nature of the study; the procedures involved; a description of any foreseeable risks or discomforts; the potential benefits (for patients); disclosure of alternative procedures or courses of treatments, if any (for patients); the extent of confidentiality of records; conditions under which the subject's participation in the study may be terminated; consequences of a patient's decision to withdraw from the study; the approximate number of subjects to be enrolled; and, whom to contact to answer pertinent questions and/or in case of research-related illness or injury. These elements of informed consent, and additional protections that apply to prisoners involved in clinical in-

vestigations, must be in conformance with the *Code of Federal Regulations* (42). Individuals who agree to be subjects in an investigation indicate their consent by signing the form or document containing the above-information.

Investigator(s) selected by the sponsor to conduct a clinical investigation must be qualified as experts by training and experience to investigate a particular drug. Each investigator's qualifications are submitted to the FDA as a part of the IND application. To participate in an investigation, each investigator signs a form agreeing to comply with and to be responsible for: ensuring that the study is conducted according to the IND's investigational plan and clinical protocol; protecting their rights, safety, and welfare of the human subjects; control of the investigational drug; written records of case histories and clinical observations; and, for the timely submission of progress reports, safety reports and a final report. It is the responsibility of the sponsor to monitor the progress of all clinical investigations under its IND. If a sponsor discovers that an investigator is not in compliance with the investigational plan, it is the sponsor's responsibility to gain compliance or to terminate the investigator's participation in the study.

Any serious, unexpected, life-threatening, or fatal adverse experience that may be associated with the use of the drug during a clinical investigation must be reported promptly to the sponsor and, subsequently, to the FDA for investigation. Depending on the severity and assessment of the adverse experience, an alert notice may be sent to other investigators, a clinical hold may be placed on the study for further evaluation and assessment, or the IND may be withdrawn by the sponsor, placed on inactive status, or terminated by the FDA.

Pre-IND Meetings

On request, the FDA will advise a sponsor on scientific, technical, or formatting concerns relating to the preparation and submission of an IND. This may include advice on the adequacy of data to support an investigational plan, the design of a clinical trial, or whether the proposed investigation is likely to produce the data needed to meet the requirements of the next step, the filing of a New Drug Application to gain approval for marketing.

FDA Review of an IND Application

The FDA's objectives in reviewing an IND are to protect the safety and rights of the human subjects

and to help ensure that the study allows the evaluation of the drug's safety and effectiveness. These objectives are best met by the accuracy and completeness of the IND submission, the design and conduct of the investigational plan, and the expertise and diligence of the investigators.

When received by the FDA, the IND submission is stamped with the date of receipt, assigned an application number, and forwarded to either the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) for review. Applications for chemical agents are sent to CDER and applications for biologics to CBER.

Within CDER, applications are forwarded to the appropriate Office of Drug Evaluation and then to one of its divisions for review as follows:

Office of Drug Evaluation I
   Division of Neuropharmacological Drug Products
   Division of Oncology Drug Products
   Division of Cardio-Renal Drug Products
Office of Drug Evaluation II
   Division of Metabolic and Endocrine Drug Products
   Division of Pulmonary Drug Products
   Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
   Division of Gastro-Intestinal and Coagulation Drug Products
   Division of Anesthetic, Critical Care, and Addiction Drug Products
   Division of Medical Imaging and Radiopharmaceutical Drug Products
Office of Drug Evaluation IV
   Division of Anti-Viral Drug Products
   Divsion of Anti-Infective Drug Products
   Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation V
   Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
   Division of Dermatologic and Dental Drug Products
   Division of Over-The-Counter Drug Products

After assignment to one of the divisions, the content of the application is thoroughly reviewed to determine whether the preclinical data indicate that the drug is sufficiently safe for administration to human subjects and that the proposed clinical studies are designed to provide the desired data on

drug safety and efficacy while not exposing the human subjects to unnecessary risks.

AUTHOR'S NOTE: *although the discussion in this chapter is based principally on the evaluation and approval of new chemical entities and prod-`ucts, for biologic products, there is a similar but necessarily distinct procedure of application review and product licensing through CBER and its divisions* (4):

Division of Allergenic Products and Parasitology
Division of Bacterial Products
Division of Viral products
Division of Vaccines and Related Products
Division of Hematologic Products
Division of Blood Establishment and Products
Division of Cellular and Gene Therapy
Division of Monoclonal Antibodies Applications

FDA Drug Classification System

Upon receipt and examination of an IND or NDA application, the FDA classifies the drug by chemical type and therapeutic potential, as shown in Table 2.1. The classification system allows the FDA to set review priorities based on the level of therapeutic advance or need (43).

Phases of a Clinical Investigation

An IND may be submitted for one or more *phases* of a clinical investigation, namely Phase 1, Phase 2 or Phase 3 (Fig. 2.2, Table 2.2). Although the phases are conducted sequentially, certain studies may overlap.

Phase 1 includes the initial introduction of an investigational drug into humans and is primarily for the purpose of assessing safety. The studies are closely monitored by clinicians expert in such investigations. The human subjects are usually healthy volunteers, although in certain protocols they may be patients. The total number of subjects included in Phase 1 studies varies with the drug, but is usually in the range of 20 to 100. The initial dose of the drug is usually low, usually one-tenth of the highest "no-effect dose" observed during the animal studies. If the first dose is well tolerated, the investigation is continued with the administration of progressively greater doses (to new subjects) until some evidence of the drug's effects are observed.

Phase 1 studies are designed to determine the human pharmacology of the drug, structure-activity

Table 2.1.   FDA Drug Classification System*

By chemical type

Type 1	New molecular entity; not marketed in the U.S.
Type 2	New ester, new salt, or other derivative of an approved active moiety
Type 3	New formulation of a drug marketed in the U.S.
Type 4	New combination of two or more compounds
Type 5	New manufacturer of a drug marketed in U.S.
Type 6	New therapeutic indication for an approved drug

Note: a drug may receive a single or multiple classification, as "3,4"

By therapeutic classification

Type P	Priority review; a therapeutic gain
Type S	A standard review; similar to other approved drugs

Additional classifications

Type AA	For treatment of AIDS or HIV-related disease
Type E	For life-threatening or severely debilitating disease
Type F	Review deferred pending data validation
Type G	Data validated, removal of "F" rating
Type N	Nonprescription drug
Type V	Drug having orphan drug status

Note: a drug may receive a single or multiple classification, as "Type P, AA, V"

*Adapted from information from Mathieu M. New drug development: a regulatory overview, 3rd ed. Cambridge, MA: PAREXEL International Corporation, 1994, and Hunter JR, Rosen DL, DeChristoforo R. How FDA expedites evaluation of drugs for AIDS and other life-threatening illnesses. Wellcome Programs in Hospital Pharmacy, No. 67930093009, 1993.

relationships, side effects associated with increasing doses, and, if possible, early evidence on effectiveness. Among the basic data collected are: the rate of the drug's absorption; the concentration of drug in the blood versus time; the rate and mechanism of drug metabolism and elimination; toxic effects, if any, in body tissues and major organs; and, changes in physiologic processes from baseline. The subjects' ability to tolerate the drug and any unpleasant effects of the drug are observed and recorded. Phase 1 studies are often useful in selecting from among different chemical analogs of a lead compound. As noted previously, capsules without excipients, are used for orally administered drugs in Phase 1 studies. If the studies demonstrate sufficient merit and if the order of drug toxicity is low, *Phase 2* is begun, using up to several hundred patients.

Phase 2 trials involve controlled clinical studies to

Table 2.2.   Phases of Clinical Testing

	Number of Patients	*Length*	*Purpose*	*Percent of Drugs Successfully Completing**
Phase 1:	20–100	Several months	Mainly safety	67
Phase 2:	Up to several hundred	Several months to 2 years	Some short-term safety, but mainly effectiveness	45
Phase 3:	Several hundred to several thousand	1–4 years	Safety, effectiveness, dosage	5–10

*For example, of 20 drugs entering clinical testing, 13 or 14 will successfully complete Phase 1 trials and go on to Phase 2; about nine will complete Phase 2 and go to Phase 3; only one or two will clear Phase 3 and, on average, about one of the original 20 will ultimately be approved for marketing. (Reference: FDA Consumer, 1987; 21: 12.)

evaluate the effectiveness of a drug in patients with the condition for which the drug is intended, and to assess side effects and risks that may be revealed. Because this phase involves the use of patients as subjects, side effects or toxicity symptoms that were not shown in the preclinical animal studies or in Phase 1 studies with healthy volunteers may be revealed for the first time. Only clinicians expert in the disease being treated are used as investigators during Phase 2 studies (Fig. 2.6). During this phase, additional data are collected on the drug's pharmacokinetics and studies undertaken to determine dose–response and dose ranging (often called *Phase 2a studies*). Each patient is monitored for the appearance of the drug's effects while the dose is carefully increased to determine the minimal effective dose. Then, the dose is extended beyond the minimally effective dose to the level at which a patient reveals extremely undesirable or intolerable toxic or adverse effects. The greater the range between the dose of drug determined to be minimally effective and that which causes severe side effects, the greater is the drug's safety margin. These dose–determination studies (often called *Phase 2b studies*) result in the specific doses and the dose range to be used in *Phase 3* studies. During Phase 2 trials, the drug product is refined with the final formulation developed for use during late Phase 2 and Phase 3 trials.

If the clinical results of Phase 2 trials indicate continued promise for the new drug and if the margin of safety appears to be good, *end-of-Phase 2* meetings between the drug's sponsor and the FDA's review division are held to analyze the data from Phases 1 and 2, to resolve any questions and issues, and to establish investigational plans for Phase 3 studies.

Phase 3 studies may include several hundred to several thousand patients in controlled and uncontrolled trials. The objective is to determine the usefulness of the drug in an expanded patient base. Many additional clinicians having patients with the condition for drug's intended use are recruited to participate in this trial. Several dosage strengths of the proposed drug may be evaluated during this phase, using formulations intended to be proposed in the NDA and for marketing. Sufficient information on the drug's effectiveness and safety is expected to be gathered during Phase 3 to evaluate the overall benefit–risk relationship of the drug and to file a complete NDA.

It is not uncommon for certain Phase 3 studies to be continued after an NDA is filed but *prior to* approval. In these instances, the completed studies (referred to as *Phase 3a* studies) are considered sufficient for the NDA. The additional studies (referred to as *Phase 3b* studies) are used to gather supplemental information which may support certain labeling requests, provide information on patients' quality of life issues, reveal product advantages over already marketed competing drugs, provide evidence in support of possible additional drug indications, or provide other clues for prospective postmarketing studies (*Phase 4*).

Clinical Study Controls and Designs

As indicated, Phase 2 and some Phase 3 studies are *controlled*, that is, the effects of the investigational drug are compared with another agent. The second agent may be a placebo (*placebo control*) or an active drug (*positive control*) as a standard drug or comparator drug product. Both a placebo and an active drug may be used as controls in the same study. For studies that are *blinded*, the identities of the investigational drug and the control(s) are not revealed to
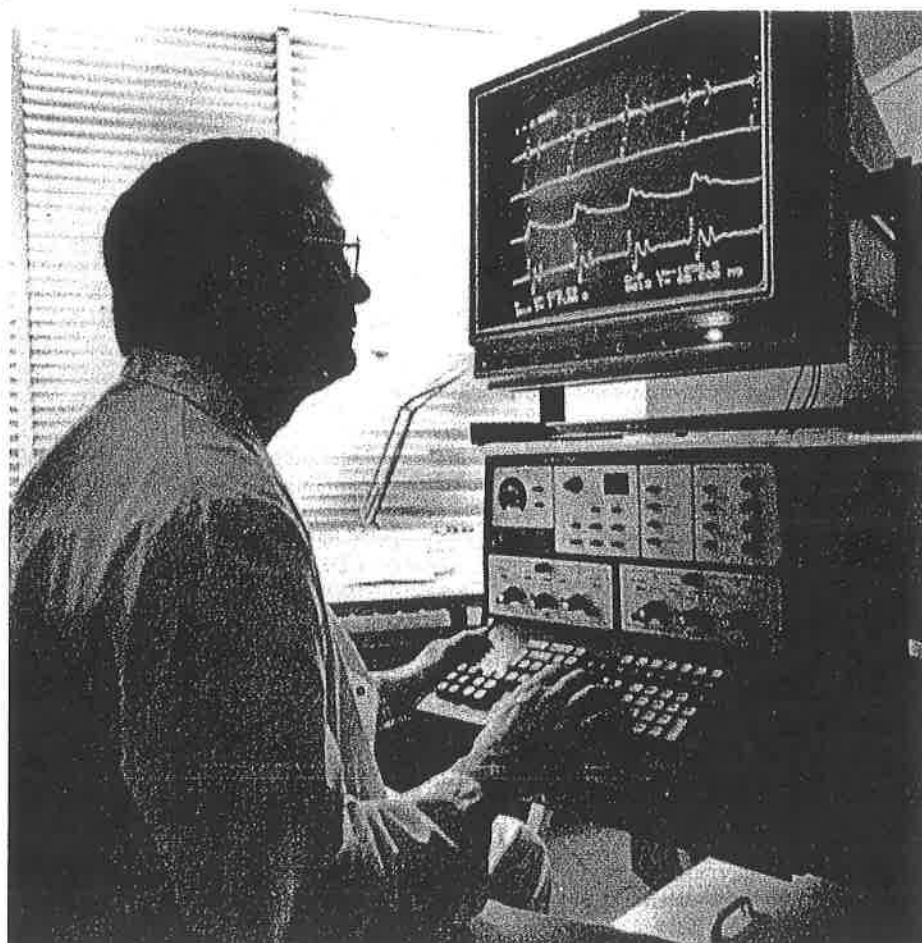
Fig. 2.6   *Monitoring the effects for cardiac function of an uninvestigational drug as a part of its clinical evaluation. (Courtesy of Eli Lilly and Company.)*

certain participants to decrease bias. In *single blind* studies, the patient is unaware of the agent administered. In *double blind* studies, neither the patient nor the clinician is aware of the agent administered. In preparing dosage forms for blinded studies, all of the agents administered, investigational drug, placebo, and/or comparator drug, must be indistinguishable to the blinded individuals. This requires the preparation of clinical trial materials of the same dosage form, having the same size, shape, color, flavor, texture, and so forth. Indistinguishable clinical trial materials are not necessary for *open label* studies in which all parties are aware of the identities of the agents administered.

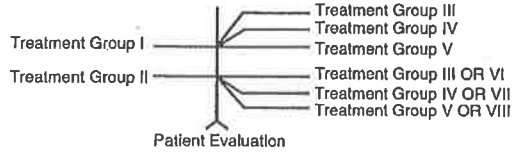In designing a clinical trial, many additional factors are considered, including the scheme of the study design and the duration of the treatment period. Before treatment, *baseline data* are obtained on each subject through physical examination and appropriate laboratory tests and procedures. Subjects randomly are assigned to different treatment groups to allow treatment comparisons. Some common parallel and crossover study designs are depicted in Figure 2.7 (44). These studies may be blinded or non-blinded using placebo and/or active drug controls. The parallel designs are applicable to most clinical trials. Crossover designs are useful in comparing different treatments within individuals since following one treatment a patient is "crossed over" to a different treatment. Between treatment periods, subjects may be given no drugs as a *washout* period to allow return to baseline.
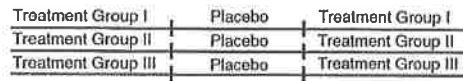
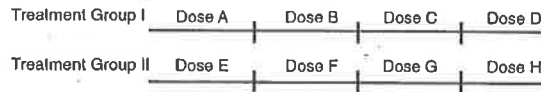## SOME CLINICAL TRIAL PARALLEL STUDY DESIGNS

1. COMMON PARALLEL DESIGNS

A. ———————— Treatment Group I
   ———————— Treatment Group II

B. ———————— Treatment Group I
   ———————— Treatment Group II
   ———————— Treatment Group III

2. TWO PART PARALLEL DESIGN

Treatment Group I ————
———————— Treatment Group III
———————— Treatment Group IV
———————— Treatment Group V

Treatment Group II ————
———————— Treatment Group III OR VI
———————— Treatment Group IV OR VII
———————— Treatment Group V OR VIII

Patient Evaluation

3. INTRODUCTION OF PLACEBO DURING TREATMENT

Treatment Group I	Placebo	Treatment Group I
Treatment Group II	Placebo	Treatment Group II
Treatment Group III	Placebo	Treatment Group III

4. MULTIPLE DOSES WITHIN EACH TREATMENT GROUP

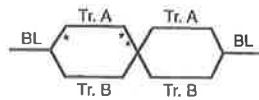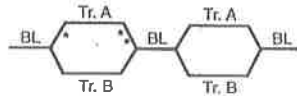| Treatment Group I	Dose A	Dose B	Dose C	Dose D
Treatment Group II	Dose E	Dose F	Dose G	Dose H

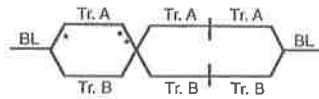## SOME CLINICAL TRIAL CROSSOVER STUDY DESIGNS

1. SINGLE CROSSOVER WITH NO INTERVENING BASELINE

2. SINGLE CROSSOVER WITH INTERVENING BASELINE

3. EXTRA PERIOD CROSSOVER

* = ascending dose   ** = descending dose

Fig. 2.7   *Some common clinical study designs.(Reprinted with permission from Spilker B. Guide to Clinical Trials, New York: Raven Press, 1991).*

Drug Dosage and Terminology

A major part of any clinical drug study is the determination of a drug's safe and effective dose. As noted earlier, dose and dose ranging studies are conducted during Phase 2 and concluded during Phase 3 clinical trials.

The safe and effective dose of a drug depends on a number of factors, including characteristics of the drug substance, the dosage form and its route of administration and a variety of patient factors including a patient's age, body weight, general health status, pathologic condition(s), and concomitant drug therapy. All of these factors and others are integral to clinical drug trials.

For convenience of dosage administration, most products are formulated to contain a drug's usual dose within a single dosage unit (e.g., capsule), or within a specified volume (e.g., 5 mL or a teaspoonful) of a liquid dosage form. To serve varying dosage requirements, manufacturers often formulate a drug into more than one dosage form and in more than a single strength.

The dose of a drug may be described as an amount that is "enough but not too much"; the idea being to achieve the drug's optimum therapeutic effect with safety but at the lowest possible dose. The effective dose of a drug may be different for different patients. The familiar bell-shaped curve, presented in Figure 2.8 shows that in a normal distribution sample, a drug's dose will provide what might be called an average effect in the majority of individuals. However, in a portion of the population the drug will produce little effect and in another portion the drug will produce an effect greater than average. The amount of drug that will produce the desired effect in the majority of adult patients is considered the drug's *usual adult dose* and would likely be the starting dose for a patient. From this initial dose the physician may, if necessary, increase or decrease subsequent doses to meet the particular requirements of the patient. Certain drugs may produce more than one effect depending on the dose administered. For example, a low dose of a barbiturate produces sedation, whereas a larger dose produces hypnotic effects. The *usual dosage range* indicates the quantitative range or amounts of the drug that may be prescribed safely within the framework of usual medical practice. Doses falling outside of the usual dosage range may result in drug underdosage or overdosage or may reflect a patient's special requirements. For drugs administered to children, a *usual pediatric dose* may be determined as discussed later in this section.

The schedule of dosage, or the *dosage regimen,* is determined during the clinical investigation and is based largely on a drug's inherent duration of action, its pharmacokinetics, and the characteristics of the dosage form (e.g., instant drug release or modified-release). Due to these factors, some drugs are recommended for once a day dosage and others more frequently.

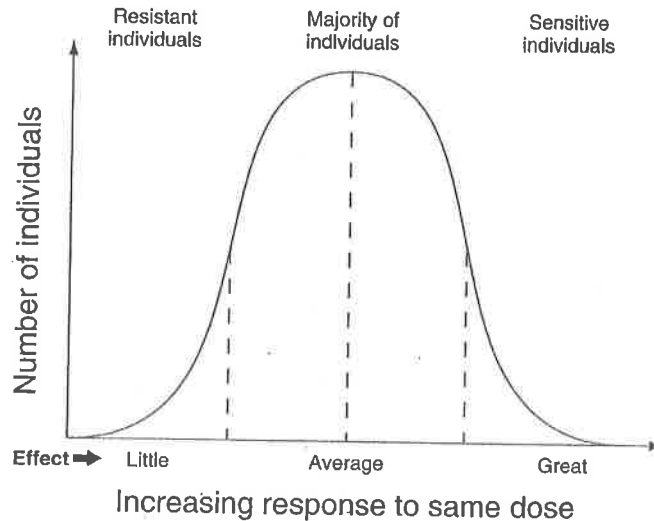For certain drugs, an *initial, priming or loading*

Fig. 2.8   *Drug effect in a population sample.*

dose may be required to attain the desired concentration of the drug in the blood or tissues, after which the blood level may be maintained through the subsequent administration of regularly scheduled *maintenance doses.*

Certain biological products, as Tetanus Immune Globulin, may have two different usual doses, one the *prophylactic dose,* or that amount administered to protect the patient from contracting the illness, and the second, the *therapeutic dose,* which is administered to a patient after exposure or contraction of the illness. The doses of vaccines and other biological products, as insulin, sometimes are expressed in *units of activity* rather than in specific quantitative amounts of the drug substance. This is due to the unavailability of suitable chemical assay methods for the active biologic component necessitating the use of biological assays to determine a product's potency.

To provide systemic effects, a drug must be absorbed from its route of administration at a suitable rate, be distributed in adequate concentration to the receptor sites, and remain there for a sufficient period. One measure of a drug's absorption characteristics is its blood serum concentration at various time intervals after administration. For certain drugs, a correlation can be made between blood serum concentration and the presentation of drug effects. For these drugs, an average blood serum concentration can be determined which represents the minimum concentration that can be expected to produce the drug's desired effects in a patient. This concentration is referred to as the *minimum effective concentration* (*MEC*). As shown in Figure 2.9, for a hypothetical drug, the serum concentration of the drug reaches the MEC 2 hours after its administration, achieves a peak concentration in 4 hours and decreases below

the MEC in 10 hours. If it would be desired to maintain the drug serum concentration above the MEC for a longer period, a second dose of the drug would be required at approximately the 8-hour time frame. The time-blood level curve presented in Figure 2.9 is hypothetical. In practice, the curve would vary, depending on the nature of the drug substance, its chemical and physical characteristics, the dosage form administered as well as individual patient factors. The second level of serum concentration of drug refers to the *minimum toxic concentration* (*MTC*). Drug serum concentrations above this level would be expected to produce dose-related toxic effects in the average individual. Ideally, the serum drug concentration in a well-dosed patient would be maintained between the MEC and the MTC (the "therapeutic window" for the drug) for the period that drug effects are desired. Table 2.3 presents examples of therapeutic, toxic, and considered lethal concentrations for some drug substances.

The *median effective dose* of a drug is that amount which will produce the desired intensity of effect in 50 percent of the individuals tested. The *median toxic dose* is that amount which will produce a defined toxic effect in 50 percent of the individuals tested. The relationship between the desired and undesired effects of a drug is commonly expressed as the *therapeutic index* and is defined as the ratio between a drug's median toxic dose and its median effective dose, TD50/ED50. Thus, a drug with a therapeutic index of 15 would be expected to have a greater margin of safety in its use than a drug with a therapeutic index of 5. For certain drugs, the therapeutic index may be as low as 2 and extreme caution must be exercised in their administration. Examples of therapeutic indices for same drugs are shown in Table 2.4.
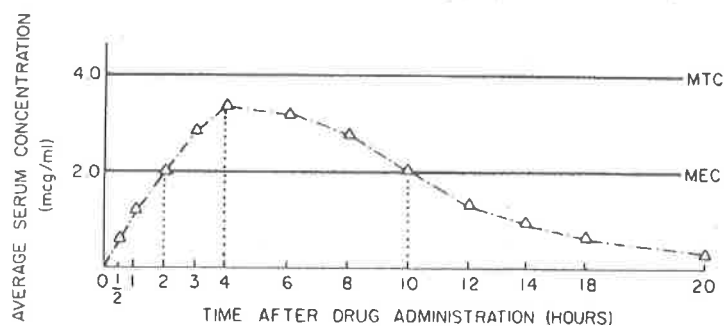

Fig. 2.9   *Example of a blood level curve for a hypothetical drug as a function of time following oral administration. MEC stands for minimum effective concentration and MTC for minimum toxic concentration.*

Table 2.3.   Examples of Therapeutic and Toxic Blood Level Concentrations of Some Drug Substances*

Drug Substance	Drug Substance Concentration, mg/liter		
	Therapeutic	Toxic	Lethal
Acetaminophen	10–20	400	1500
Amitriptyline	0.5–0.20	0.4	10–20
Barbiturates:			
short acting	1	7	10
intermediate acting	1–5	10–30	30
long acting	~10	40–60	80–150
Dextropropoxyphene	0.05–0.2	5–10	57
Diazepam	0.5–2.5	5–20	>50
Digoxin	0.0006–0.0013	0.002–0.009	—
Imipramine	0.05–0.16	0.7	2
Lidocaine	1.2–5.0	6	—
Lithium	4.2–8.3	13.9	13.9–34.7
Meperidine	0.6–0.65	5	30
Morphine	0.1	—	0.05–4
Phenytoin	5–22	50	100
Quinidine	3–6	10	30–50
Theophylline	20–100	—	—

*Adapted from Winek CL. Clin Chem 1976;22:832; and Goth A. Medical Pharmacology, 11th ed. St. Louis: C.V. Mosby Co., 1984;757–759.

Some patient factors considered in determining a drug's dose in clinical investigations and in medical practice include the following.

Age

The age of the patient may be a consideration in the determination of drug dosage. Age is particularly important in the treatment of neonatal, pediatric, and geriatric patients. Infants, especially newborn and those born prematurely, have immature hepatic and renal function by which drugs are normally inactivated and eliminated from the body. A reduced capacity to detoxify and eliminate drugs can result in drug accumulation in the tissues to toxic levels. Often, drug blood levels are determined in these patients and carefully monitored.

Before there was sufficient understanding of the capacity of the pediatric patient to detoxify and eliminate drugs, infants and children were dosed by fractions of the adult dose determined by an age-based formula. Age alone is no longer considered to be a singularly valid criterion in the determination of pediatric dosage. Today, doses for many drugs are determined through pediatric clinical trials under special protocols and subject safeguards (45). Many pediatric doses are based on body weight or body surface area as noted later in this section.

Elderly persons also present unique therapeutic and dosing problems that require special attention.

Most physiologic functions begin to diminish in adults after the third decade of life. For example, cardiac output declines approximately 1 percent per year from age 20 to age 80. Glomerular filtration rate falls progressively until at age 80, to only about half of what it was at age 20. There is also a decrease in vital capacity, immune capacity and liver microsomal enzyme function (46). The decline in renal and hepatic function in the elderly slows the drug clearance rate and increases the possibil-

Table 2.4.   Examples of Therapeutic Indices for Various Drug Substances*

Drug Substances with Therapeutic Indices		
Less than 5	Between 5 and 10	Greater than 10
Amitriptyline	Barbiturates	Acetaminophen
Chlordiazepoxide	Diazepam	Bromide
Diphenhydramine	Digoxin	Chloral hydrate
Ethchlorvynol	Imipramine	Glutethimide
Lidocaine	Meperidine	Meprobamate
Methadone	Paraldehyde	Nortriptyline
Procainamide	Primodone	Pentazocine
Quinidine	Thioridazine	Propoxyphene

*Reprinted with permission from Niazi S. Textbook of Biopharmaceutics and Clinical Pharmacokinetics. New York: Appleton-Century-Crofts, 1979;254.

ity of drug accumulation and toxicity. Elderly persons may also respond differently to drugs than younger patients because of changes in drug-receptor sensitivity or because of age-related alterations in target tissues or organs (47).

Further, the chronic disorders present in the majority of geriatric patients requires concomitant drug therapy, increasing the possibility of drug–drug interactions, and adverse drug effects. In the clinical evaluation of a new drug, consideration is given to other drugs most likely to be taken concomitantly by the intended patient, with studies directed toward determining potential drug-drug effects or interactions.

To assist the pharmacist in pediatric and geriatric patient dosing, the American Pharmaceutical Association publishes the *Pediatric Dosage Handbook* and the *Geriatric Dosage Handbook* (48).

Body Weight

The usual doses for drugs are considered generally suitable for 70 kg (150 pound) individuals. The ratio between the amount of drug administered and the size of the body influences drug concentration in body fluids. Therefore, drug dosage may require adjustment from the usual adult dose for abnormally lean or heavy patients. The doses for certain drugs are determined based on body weight and are expressed on a *milligram* (drug) *per kilogram* (body weight) basis (e.g., 1 mg/kg).

As noted earlier, drug dosage for youngsters based on body weight is considered more dependable than that based strictly on age and for many drugs the dose is determined on a mg/kg basis. In some instances, a pediatric dose may be based on a combination of age and weight (e.g., 6 months to 2 years of age—3 mg/kg/ day).

Body Surface Area

Due to the correlation that exists between a number of physiological processes and body surface area (BSA), some drug doses are determined based on this relationship (e.g., 1 mg/M² BSA). The body surface area for a child or an adult may be determined using a nomogram (Fig. 2.10). The BSA is determined at the intersect of a straight line drawn to connect an individual's height and weight. For example, an adult measuring 67 inches in height and weighing 132 pounds would have a BSA of approximately 1.7 square meters.

Sex

Because men and women have different responses to certain drugs and drug dosages due to biochemical and physiologic factors, both sexes should be included in clinical drug trials. Pharmacokinetic differences between women and men may be particularly important for drugs having a narrow therapeutic index (NTI), in which the smaller average size of women might necessitate modified dosing. Drugs with narrow therapeutic indices carry the inherent risk that drug blood levels may increase to toxic levels or decrease to ineffective levels with minimal dosing changes. Other important female gender studies include the effects of the menstrual cycle and menopausal status on a drug's pharmacokinetics and the drug interaction potential of concomitant estrogen or oral contraceptive use (49).
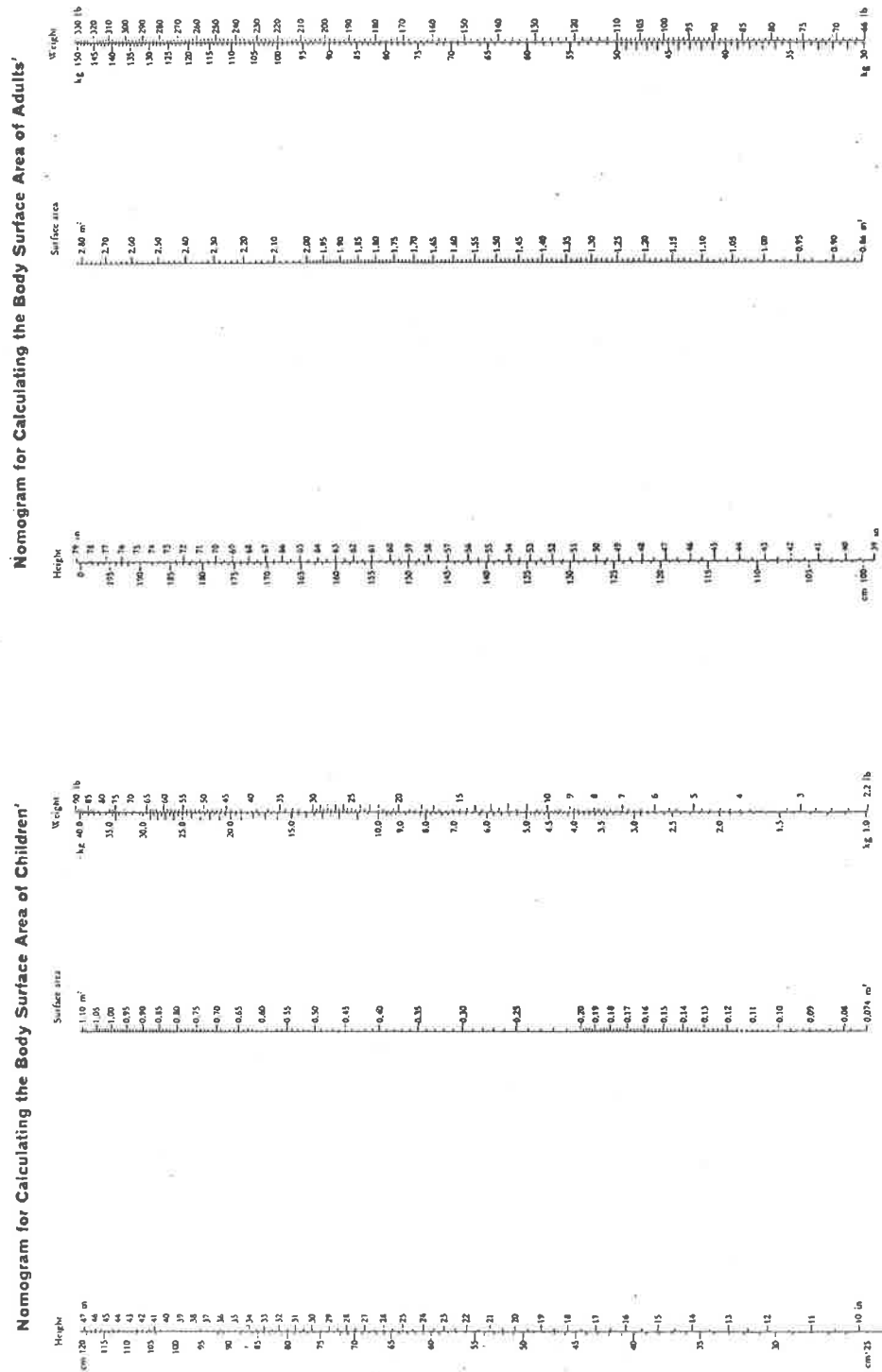
Because virtually all clinical investigations have not included pregnant women in their study protocols, and thus drug effects are undetermined in these circumstances, great caution is advised for most drugs' use during pregnancy and in women of child-bearing age. A similar caution is applicable to drug use in nursing mothers because the transfer of drugs from mother's milk to an infant is well documented for a variety of drugs with drug effects (50–51).

Pathologic State

The effects of certain drugs may be modified by the pathologic condition of the patient. For example, if certain drugs are used in the presence of renal impairment, excessive systemic accumulation of the drug may occur with possible toxicity. Under such conditions, lower than usual doses are indicated, and if therapy is prolonged, blood serum levels of the drug should be taken and the patient monitored at regular intervals to assure the maintenance of non-toxic levels of the drug. In these instances, pharmacokinetic dosing is an integral part of the clinical study protocol and of approved product labeling.

Tolerance

The ability to endure the influence of a drug, particularly when acquired by a continued use of the substance, is referred to as *drug tolerance*. It is usually developed to a specific drug and to its chemical congeners; in the latter instance, it is referred to as *cross-tolerance*. The result is that drug dosage must be increased over time to maintain a desired therapeutic response. Tolerance is common with the use of antihistamines and narcotic analgesics. After the development of tolerance, normal response may be regained by suspending the drug's administration for a period of time.

Nomogram for Calculating the Body Surface Area of Adults'

Nomogram for Calculating the Body Surface Area of Children'

'From the formula of DeBois and DeBois, *Arch Intern. Med.*,17, 863 1916 $S = W^{0.425} \times H^{0.725} \times 71.84$ or log $S = 0.425$ log $W + 0.725$ log $H + 1.8564$ where S = body surface area in square centimeters, W = weight in kilograms, H = height in centimeters

Fig. 2.10   *Nomograms for calculating body surface area. (Reprinted with permission from R.J. Geigy S.A. Documenta Geigy Scientific Tables, 6th ed., pp. 632–633.)*

Concomitant Drug Therapy

The effects of a drug may be modified by the prior or concurrent administration of another drug. Such interference between drugs is referred to as a *drug–drug interaction* and may be due to a chemical or physical interaction between the drugs or to an alteration of the absorption, distribution, metabolism, or excretion patterns of one of the drugs. Certain clinical protocols include the evaluation of a new drug in the presence of other drugs most likely to be included in the target patient's therapeutic regimen.

Important drug–drug interactions that are identified during a drug's clinical trials are included in approved product labeling. Additional drug interactions that become known after the drug is marketed are added in labeling revisions. Drug–drug interactions may include "social" agents such as tobacco and alcohol, which affect the pharmacokinetics of a number of drugs and require an alteration in a drug's usual dose.

Time and Conditions of Administration

The time at which a drug is administered may influence dosage. This is especially true for oral therapy in relation to meals. Absorption proceeds more rapidly if the stomach and upper portions of the intestinal tract are empty of food. A dose of a drug that is effective when taken before a meal may be less effective if administered during or after eating. Drug–food interactions can affect a drug's usual absorption pattern. When such interactions are determined, appropriate guidance is provided in the product literature.

Dosage Form and Route of Administration

The effective dose of a drug may vary, depending on the dosage form and the route of administration. Drugs administered intravenously enter the blood stream directly and completely. In contrast, drugs administered orally are rarely, if ever, fully absorbed into the bloodstream due to the various physical, chemical, and biologic barriers to their absorption. Thus, in many instances, a lower parenteral (injectable) dose of a drug is required than the oral dose to achieve the same blood levels or clinical effects. Varying rates and degrees of absorption can occur from drug administration from the rectum, gastrointestinal tract, sublingually, via the skin and from other sites. Therefore for a given drug, different dosage forms and routes of administration are considered "new" by the FDA and must be evaluated individually through clinical studies to determine the effective doses.

"Treatment IND"

A *Treatment IND* or a *treatment protocol* permits the use of an investigational drug in the treatment of patients *not enrolled* in the clinical study but who have a serious or immediately life-threatening disease for which there is no satisfactory alternative therapy. The objective is to make promising new drugs available to desperately ill patients as early as possible in the drug development process. By FDA definition, *"immediately life-threatening"* means "a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment" (1). This would include such conditions as advanced cases of AIDS, herpes simplex encephalitis, advanced metastatic refractory cancers, bacterial endocarditis, Alzheimer's disease, advanced multiple sclerosis, advanced Parkinson's disease, and others.

For products to be considered for a Treatment IND, the drug must be under active investigation in a controlled clinical trial with sufficient evidence of its safety and efficacy demonstrated to support its use in the intended patients. Depending on the sponsor's clinical safety and efficacy data, a drug may be approved for "treatment use" during Phase 2 or Phase 3 of the clinical trials. In applying for a drug's treatment use, a sponsor must submit a *treatment protocol* in addition to the information normally included in an IND application. In making its decision, the FDA renders a risk–benefit judgment after considering the severity of the disease, any alternative therapy, and the potential benefits of the drug against the known and potential risks. In addition to the treatment IND, there is also provision in the law for the *emergency use* of an investigational drug in rare situations before a sponsor's submission of an IND application (1).

IND for an Orphan Drug

Under the Orphan Drug Act of 1983 as amended, an *orphan disease* is defined as a rare disease or condition that affects fewer than 200,000 people in the United States and for which there is no reasonable expectation that costs of research and development for the indication can be recovered by sales of the product in the United States. Examples of such illnesses are chronic lymphocytic leukemia, Gaucher's disease, cystic fibrosis, and conditions related to acquired immune deficiency syndrome (AIDS).

The FDA Office of Orphan Products Development was established to identify and facilitate the

development of orphan products, including drugs, biologics, and medical devices. To foster the necessary research and development, the FDA provides support grants to conduct clinical trials on safety and effectiveness. Applicants first request orphan status designation for the disease and file an IND or an investigational device exemption (IDE) with their grant application. In most cases, grants are awarded for Phase 2 and Phase 3 clinical studies based on preliminary clinical research. Regular and Treatment IND protocols may be included in orphan drug clinical trials. An incentive to orphan product development is a provision for a 7-year period of exclusive marketing rights after regulatory approval of a product.

Withdrawal or Termination of an IND

A sponsor may withdraw an IND at any time ending all clinical investigations. All stock of clinical supplies must be returned to the sponsor or otherwise destroyed. If an IND is withdrawn because of safety reasons, the FDA, IRB, and all investigators must be so advised.

If no subjects are entered in an IND for a period of two years or more or if investigations remain on a clinical hold for one year or more, the FDA may place the IND on "inactive status," upon proper notification of the sponsor. An IND may also be placed on inactive status on the initiative of the sponsor.

The FDA may terminate an IND and end related clinical investigations based on safety, efficacy, or regulatory compliance issues.

The New Drug Application (NDA)

If the three phases of clinical testing during the IND period demonstrate sufficient drug safety and therapeutic effectiveness, the sponsor may file a New Drug Application (NDA) with the Food and Drug Administration. This filing may be preceded by a pre-NDA meeting between the sponsor and the FDA to discuss the content and format of the new drug application. The purpose of the NDA is to gain permission to market the drug product in the United States.

General Content of the NDA Submission

An NDA application contains a complete presentation of all of the preclinical and clinical results that the sponsor has obtained during investigation

of the drug. It is a highly organized document that may contain several hundred volumes of information. In recent years, a computer-assisted new drug application (CANDA) process has been implemented whereby the sponsor may interact by computer with the FDA reviewers to facilitate the application review process.

The applicant submits three copies of the NDA: an *archival copy*, maintained by the FDA as the reference document; a *review copy*, used by the FDA review division, and a *field copy*, used by the FDA district office and field inspectors in an on-site *pre-approval inspection* (1). The pre-approval inspection is conducted in the facilities in which the approved product is to be produced. The inspectors assess the sponsor's capability to comply with all control and quality standards contained in the application including the FDA's Current Good Manufacturing Practice (CGMP) standards (discussed in Chapter 5). Final approval of an NDA can be contingent upon this inspection.

In part, an application for a new chemical entity contains the following components:

- Application form (Form FDA 356h) with the name, address, date, and signature of the applicant or of the applicant's authorized representative;
- Chemical, nonproprietary, code and proprietary names of the drug, the dosage form, its strength, and route of administration;
- Statement regarding the applicant's proposal to market the drug product as a prescription-only, or, as an OTC product;
- Detailed summary of all aspects of the application, including the proposed text of the product's intended labeling, chemistry, manufacturing and controls, nonclinical and clinical pharmacology and toxicology, human pharmacokinetics and bioavailability, statistical analysis, clinical trial data, benefit and risk considerations, and proposed additional or planned postmarketing studies;
- Detailed technical sections on the chemistry, manufacturing and controls for the drug substance, including its physical and chemical characteristics, methods of identification, assay, and controls and the drug product, including its composition, specifications, methods of manufacture and equipment used, in-process controls, batch and master production records, container and closure systems, stability, and expiration dating;
- Detailed technical sections for nonclinical pharmacology and toxicology in relation to the pro-

posed therapeutic indication, including acute, subacute, and chronic toxicology, carcinogenicity, reproductive toxicology, and animal studies of absorption, distribution, metabolism, and excretion;

- Detailed technical sections for human pharmacokinetics and bioavailabilty, and microbiology for antibiotic applications;
- Detailed technical sections for clinical data for each controlled and uncontrolled study relating to the proposed indication, a copy of the study protocol, effectiveness and safety data including any updates on safety information, comparison of human and animal pharmacology and toxicology data, support for the dosage and dose intervals and modifications for specific subgroups, as pediatrics, geriatrics, and renally impaired;
- Statement regarding compliance to IRB and informed consent requirements;
- Statistical methods and analysis of the clinical data;
- Samples of the drug substance, drug product proposed for marketing, reference standards, and finished market package, as requested; and
- Clinical case report forms for the archival copy of the application.

The FDA accepts foreign clinical data if they are applicable to the United States population and domestic medical practice; if the studies were conducted by clinical investigators of recognized competence; and, if the FDA considers the data to be valid without the need for an on-site inspection. The FDA has entered into certain bilateral agreements with some countries whereby inspections performed by regulatory personnel of those countries are acceptable to the FDA.

Drug Product Labeling

The labeling of all drug products distributed in the United States must meet the specific labeling requirements set forth in *Code of Federal Regulations* and approved for each product by the Food and Drug Administration (52). Specific labeling requirements differ for prescription drugs, nonprescription drugs, and animal drugs. In each instance, however, the objective is the same—to ensure the appropriate and safe use of the approved product.

According to federal regulations, *drug labeling* includes not only the labels placed on an immediate container but also the information on the packaging, in package inserts, and in company literature, advertising, and promotional materials.

For prescription drugs, labeling represents a summary of all of the preclinical and clinical studies conducted over the period of years from drug discovery through product development to FDA approval. The essential prescribing information for a human prescription drug is provided in the package insert, which by law contains a balanced presentation of the usefulness and the risks associated with the product to enable safe and effective use. The package insert is required to contain the following summary information in the order listed.

1. *Description* of the product, including the proprietary and nonproprietary names, dosage form and route of administration, quantitative product composition, pharmacologic or therapeutic class of the drug, chemical name and structural formula of the drug compound, and important chemical and physical information (pH, sterility, etc.).
2. *Clinical Pharmacology,* including a summary of actions of the drug in humans, relevant in-vitro and animal studies essential to the biochemical and/or physiological basis for action, pharmacokinetic information on rate and degree of absorption, biotransformation and metabolite formation, degree of drug binding to plasma proteins, rate or half-time of elimination, uptake by a particular organ or fetus, and any toxic effects.
3. *Indications and Usage,* including the FDA-approved indications in the treatment, prevention, or diagnosis of a disease or condition, evidence of effectiveness demonstrated by results of controlled clinical trials, special conditions to the drug's use for short-term or long-term use.
4. *Contraindications,* stating those situations in which the drug should not be used because the risk of use clearly outweighs any possible beneficial effect. Included are contraindications associated with drug hypersensitivity, concomitant therapy, disease state, and/or factors of age or gender.
5. *Warnings,* including descriptions of serious adverse reactions and potential safety hazards, limitations to use imposed by them, and steps to be taken if they occur.
6. *Precautions,* including special care to be exercised by prescriber and patient in the use of the drug; e.g., drug/drug, drug/food, drug/laboratory test interactions, effects on fertility, use in pregnancy, use in nursing mothers, and in pediatric patients.
7. *Adverse Reactions,* including predictable and potential unpredictable undesired (side) effects, categorized by organ system or severity of reaction and frequency of occurrence.

the marketing of the product during a review period; issue a product recall notice; or withdraw product approval for marketing.

In the event of information on, or a confirmed incident of, a mislabeled, contaminated, or deteriorated product in distribution, the sponsor is required to file an "NDA-Field Alert Report" to the FDA District office· by telephone or other rapid communication within 3 working days of receipt of the information. The FDA follows up with appropriate action.

Annual Reports

Each year the sponsor of an approved drug must file, with the FDA division responsible for the NDA review, a report containing the following information: an annual summary of significant new information that might affect the safety, effectiveness, or labeling of the drug product; data on the quantity of dosage units of the drug product distributed domestically and abroad; a sample of currently used professional labeling, patient brochures, or package inserts, and a summary of any changes since the previous report; reports of experiences, investigations, studies, or tests involving chemical or physical properties of the drug that may affect its safety or effectiveness; a full description of any manufacturing and controls changes (not requiring a Supplemental New Drug Application); copies of unpublished reports and summaries of published reports of new toxicologic findings in vitro and animal studies conducted or obtained by the sponsor; full or abstract reports on published clinical trials of the drug, including studies on safety and effectiveness; new uses; biopharmaceutic, pharmacokinetic, clinical pharmacologic, and epidemiologic reports; pharmacotherapeutic and lay press articles on the drug; summaries of unpublished clinical trials or prepublication manuscripts, as available, conducted or obtained by the sponsor; a statement on the current status of any postmarketing studies performed by, or on behalf of, the sponsor; and specimens of mailing pieces or other forms of promotion of the drug product. Failure to make required reports may lead to FDA withdrawal of approval for marketing.

Supplemental, Abbreviated, and Other Applications

In addition to the IND and NDA the following types of applications are filed with the FDA for the purposes described.

Supplemental New Drug Application (SNDA)

A sponsor of an approved NDA may make changes in that application through the filing of a Supplemental New Drug Application (SNDA). Depending on the changes proposed, some require FDA approval before implementing; others do not.

Among the changes requiring prior approval are: a change in the method of synthesis of the drug substance; use of a different facility to manufacture the drug substance where the facility has not been approved through inspection for Current Good Manufacturing Practice standards within the previous 2 years; change in the formulation, analytical standards, method of manufacture, or in-process controls of the drug product; use of a different facility or contractor to manufacture, process, or package the drug product; change in the container and closure system for a drug product; extension of the expiration date for a drug product based on new stability data; any labeling change that does not add to or strengthen a previously approved label statement.

Examples of changes that may be made without prior approval are: minor editorial or other changes in the labeling that add to or strengthen an approved label section; any analytical changes made to comply with the USP/NF; an extension of the product's expiration date based on full shelf-life data obtained from a protocol in the approved application; and a change in the size (not the type of system) of the container for a solid dosage form.

Abbreviated New Drug Application (ANDA)

An Abbreviated New Drug Application (ANDA) is one in which nonclinical laboratory studies and clinical investigations may be omitted, except those pertaining to the drug's bioavailability. These applications are usually filed for duplicates (generic copies) of drug products previously approved under a full NDA, and for which the FDA has determined that information on the exempted nonclinical and clinical studies is already available at the agency. ANDAs commonly are filed by competing companies following the expiration of patent term protection of the innovator drug/drug product. Bioavailability and product bioequivalency are discussed in Chapter 4.

Biologics License Application (BLA)

Biologics License Applications (BLAs) are submitted to the FDA's Center for Biologics Evaluation

8. *Drug Abuse and Dependence*, including legal schedule if a controlled substance, types of abuse and resultant adverse reactions, psychological and physical dependence potential, and treatment of withdrawal.
9. *Overdosage*, including signs, symptoms, and laboratory findings of acute overdosage, along with specifics or general principles of treatment.
10. *Dosage and Administration*, stating the recommended usual dose, the usual dosage range, the safe upper limit of dosage, duration of treatment, modification of dosage in special patient populations (children, elders, patients with kidney and/or liver dysfunction), and special rates of administration (as with parenteral medications).
11. *How Supplied*, including information on available dosage forms, strengths, and means of dosage form identification, as color, coating, scoring, and National Drug Code.

FDA Review and "Action Letters"

The completed New Drug Application is carefully reviewed by the Food and Drug Administration, which decides whether to allow the sponsor to market the drug, to disallow marketing, or to require additional data before rendering a judgment. By regulation, the FDA must respond within 180 days of receipt of an application. This 180-day period is called the *review clock* and is often extended by mutual agreement between the applicant and the FDA, as additional information, studies, or clarifications are sought.

The NDA is reviewed by the same FDA division that reviewed the sponsor's original IND. However, for the NDA review, the FDA also obtains the recommendation of an outside Advisory Review Committee, comprised of persons of recognized competence and stature in the clinical area of the proposed drug's use. Although not binding, this committee's recommendation has influence in the FDA's decision to issue one of the following action letters after the entire review of the application is completed.

Approvable Letter. The agency will approve the application if specific additional data or other requested material is submitted, or specified conditions are met. This frequently pertains to development or wording of the final product labeling.

Approval Letter. Approval of the application permitting marketing.

Not Approvable Letter. The application is not considered approvable because of one or more deficiencies.

After an NDA is approved and the product marketed, the FDA requires periodic safety and other reports, schedules plant inspections, and requires continued compliance with control and quality standards and current good manufacturing practices.

Phase 4 Studies and Postmarketing Surveillance

The receipt of marketing status for a new drug product does not necessarily end a sponsor's investigation of the drug. Continued clinical investigations, often referred to as Phase 4 studies, may contribute to the understanding of the drug's mechanism or scope of action; may indicate possible new therapeutic uses for the drug; and/or may demonstrate the need for additional dosage strengths, dosage forms or routes of administration. Postmarketing studies may also reveal additional side effects, serious and unexpected adverse drug effects, and/or drug interactions.

In applying for a new use, strength, dosage form, or route of administration for a previously approved drug, the sponsor must file a new IND, conduct all necessary additional nonclinical and clinical studies, and file a new NDA for FDA review.

Postmarketing Reporting of Adverse Drug Experiences

A drug's sponsor is required to report to the FDA each adverse drug experience that is both serious (life-threatening or fatal) and unexpected (not contained in the approved drug product labeling) regardless of the source of the information within 15 working days of receipt of the information. These "15-day Alert" reports must then be investigated by the sponsor with a follow-up report submitted to the FDA, again within 15 working days. Other adverse experiences, not considered serious and unexpected, are reported on a quarterly basis for three years following the date of approval of the NDA and then annually thereafter. Practicing pharmacists and other health care professionals participate in adverse drug experience reporting through the FDA's "MedWatch" program, using forms provided for this purpose (53).

Depending on the nature, causal relationship, and seriousness of an adverse drug reaction (ADR) report, the FDA may require revised product labeling to reflect the new findings; ask the sponsor to issue special warning notices to health care professionals; undertake or require the sponsor to undertake a review of all available clinical data; restrict

and Research (CBER) for the manufacture of biologicals, as blood products, vaccines, and toxins. The applications for biologics approvals follow the regulatory requirements as stated specifically for these products in the relevant parts of the *Code of Federal Regulations* (4).

Animal Drug Applications

The Federal Food, Drug, and Cosmetic Act, as amended, contains specific regulations pertaining to the approval for the marketing and labeling of drugs intended for animal use (6). Regulations apply to Investigational New Animal Drug Applications (INADA), New Animal Drug Applications (NADA), Supplemental New Animal Drug Applications (SNADA) and Abbreviated New Animal Drug Applications (ANADA).

Medical Devices

The Food and Drug Administration has regulatory authority over the manufacture and licensing of all medical devices, from surgeon's gloves and catheters to cardiac pacemakers and cardiopulmonary bypass blood gas monitors (7). Included in the regulations are standards and procedures for manufacturer registration, investigational studies, good manufacturing practices, and premarket approval.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

In recognition of the international marketplace for pharmaceuticals and in an effort to achieve global efficiencies for both regulatory agencies and the pharmaceutical industry, the FDA, counterpart agencies of the European Union and Japan, and geographic representatives of the pharmaceutical industry formed a tripartite organization in 1991 to discuss, identify, and address relevant regulatory issues. This organization, named the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has worked toward "harmonizing" or bringing together regulatory requirements with the long range goal of establishing a uniform set of standards for drug registration within these geographic areas.

With ICH success, duplicative technical requirements for registering pharmaceuticals would be eliminated; new drug approvals would occur more rapidly; patient access to new medicines would be enhanced worldwide; the quality, safety and efficacy of imported products would be improved; and there would be an increase in information transfer between participating countries (54–55).

The ICH's work toward uniform standards is focused in three general areas: drug/drug product quality, safety, and efficacy.

The quality topics include stability, light stability, analytical validation, impurities, and biotechnology. The safety topics include carcinogenicity, genotoxicity, toxicokinetics, reproduction toxicity, and single and repeat dose toxicity. The efficacy topics include population exposure, managing clinical trials, clinical study reports, dose response, ethnic factors, good clinical practices, and geriatrics. For each topic, relevant regulations are identified, addressed, and consensus guidelines developed. The intention is that these guidelines will be incorporated into domestic regulations. In the United States, the resulting guidelines are published in the *Federal Register* as "Notices," with accompanying statements indicating that the guideline should be "useful" or "considered" by applicants conducting required studies or submitting registration applications. Examples of specific ICH-developed guidelines include:

Stability Testing of New Drug Substances and Products

Validation of Analytical Procedures for Pharmaceuticals

Impurities in New Drug Substances

Impurities in New Drug Products

Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

Preclinical Testing of Biotechnology-Derived Pharmaceuticals

General Considerations for Clinical Trials

Studies in Support of Special Populations: Geriatrics

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3

DOSAGE FORM DESIGN: PHARMACEUTIC AND FORMULATION CONSIDERATIONS

Chapter at a Glance

DRUG SUBSTANCES are seldom administered alone, but rather as part of a formulation in combination with one or more nonmedical agents that serve varied and specialized pharmaceutical functions. Through selective use of these nonmedicinal agents, referred to as *pharmaceutic ingredients*, dosage forms of various types result. The pharmaceutic ingredients solubilize, suspend, thicken, dilute, emulsify, stabilize, preserve, color, flavor, and fashion medicinal agents into efficacious and appealing dosage forms. Each type of dosage form is unique in its physical and pharmaceutical characteristics. These varied preparations provide the manufacturing and compounding pharmacist with the challenges of formulation and the physician with the choice of drug and drug delivery system to prescribe. The general area of study concerned with the formulation, manufacture, stability, and effectiveness of pharmaceutical dosage forms is termed *pharmaceutics*.

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all of the drug

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substances and pharmaceutic ingredients to be used in fabricating the product. The drug and pharmaceutic materials utilized must be compatible with one another to produce a drug product that is stable, efficacious, attractive, easy to administer and safe. The product should be manufactured under appropriate measures of quality control and packaged in containers that contribute to product stability. The product should be labeled to promote correct use and be stored under conditions that contribute to maximum shelf life.

Methods for the preparation of specific types of dosage forms and drug delivery systems are described in subsequent chapters. This chapter presents some general considerations regarding physical pharmacy, drug product formulation and pharmaceutic ingredients.

The Need for Dosage Forms

The potent nature and low dosage of most of the drugs in use today precludes any expectation that the general public could safely obtain the appropriate dose of a drug from the bulk material. The vast majority of drug substances are administered in milligram quantities, much too small to be weighed on anything but a sensitive laboratory balance. For instance, how could the layperson accurately obtain the 325 mg of aspirin found in the common aspirin tablet from a bulk supply of aspirin? It couldn't be done. Yet, compared with many other drugs, the dose of aspirin is formidable (Table 3.1). For example, the dose of ethinyl estradiol, 0.05 mg, is 1/6500 the amount of aspirin in an aspirin tablet. To put it another way, 6500 ethinyl estradiol tablets, each containing 0.05 mg of drug, could be made from an amount of ethinyl estradiol equal to the amount of aspirin in just one 325 mg aspirin tablet. When the dose of the drug is minute, as that for ethinyl estradiol, solid dosage forms such as tablets and capsules must be prepared with fillers or diluents so that the size of the resultant dosage unit is large enough to pick up with the fingertips.

Besides providing the mechanism for the safe and convenient delivery of accurate dosage, dosage forms are needed for additional reasons:

1. For the protection of a drug substance from the destructive influences of atmospheric oxygen or humidity (e.g., coated tablets, sealed ampuls)
2. For the protection of a drug substance from the destructive influence of gastric acid after oral administration (e.g., enteric-coated tablets)

Table 3.1. Examples of Some Drugs with Relatively Low Usual Doses

Drug	Usual Dose, mg	Category
Betaxolol HCl	10	Antianginal
Clotrimizole	10	Antifungal
Methylphenidate HCl	10	CNS Stimulant
Medroxyprogesterone acetate	10	Progestin
Mesoridazine besylate	10	Antipsychotic
Morphine Sulfate	10	Narcotic analgesic
Nifedipine	10	Coronary vasodilator
Omeprazole	10	Antiulcer
Quinapril HCl	10	Antihypertensive
Chlorazepate dipotassium	7.5	Tranquilizer
Buspirone HCl	5	Antianxiety
Enalapril maleate	5	Antihypertensive
Hydrocodone	5	Narcotic analgesic
Prednisolone	5	Adrenocortical steroid
Albuterol sulfate	4	Bronchodilator
Chlorpheniramine Maleate	4	Antihistaminic
Felodipine	2.5	Vasodilator
Glyburide	2.5	Antidiabetic
Doxazosin mesylate	2	Antihypertensive
Levorphanol tartrate	2	Narcotic analgesic
Prazosin HCl	2	Antihypertensive
Risperidone	2	Antipsychotic
Estropipate	1.25	Estrogen
Bumetanide	1	Diuretic
Clonazepam	1	Anticonvulsant
Ergoloid mesylates	1	Cognitive adjuvant
Alprazolam	0.5	Antianxiety
Colchicine	0.5	Gout suppressant
Nitroglycerin	0.4	Antianginal
Digoxin	0.25	Cardiotonic (maintenance)
Levothyroxine	0.1	Thyroid
Misoprostol	0.1	Antiulcerative
Ethinyl Estradiol	0.05	Estrogen

3. To conceal the bitter, salty, or offensive taste or odor of a drug substance (e.g., capsules, coated tablets, flavored syrups)
4. To provide liquid preparations of substances that are either insoluble or unstable in the desired vehicle (e.g., suspensions)
5. To provide clear liquid dosage forms of substances (e.g., syrups, solutions)
6. To provide rate-controlled drug action (e.g., various controlled-release tablets, capsules, and suspensions)

7. To provide optimal drug action from topical administration sites (e.g., ointments, creams, transdermal patches, ophthalmic, ear, and nasal preparations)
8. To provide for the insertion of a drug into one of the body's orifices (e.g., rectal or vaginal suppositories)
9. To provide for the placement of drugs directly into the bloodstream or into body tissues (e.g., injections)
10. To provide for optimal drug action through inhalation therapy (e.g., inhalants and inhalation aerosols)

General Considerations in Dosage Form Design

Before formulating a drug substance into a dosage form, the desired product type must be determined insofar as possible to establish the framework for product development activities. Then, various initial formulations of the product are developed and examined for desired features (e.g., drug release profile, bioavailability, clinical effectiveness) and for pilot plant studies and production scale-up. The formulation that best meets the goals for the product is selected and represents its *master formula*. Each batch of product subsequently prepared must meet the specifications established in the master formula.

There are many different forms into which a medicinal agent may be placed for the convenient and efficacious treatment of disease. Most commonly, a pharmaceutical manufacturer prepares a drug substance in several dosage forms and strengths for the efficacious and convenient treatment of disease (Fig. 3.1). Before a medicinal agent is formulated into one or more dosage forms, among the factors considered are such therapeutic
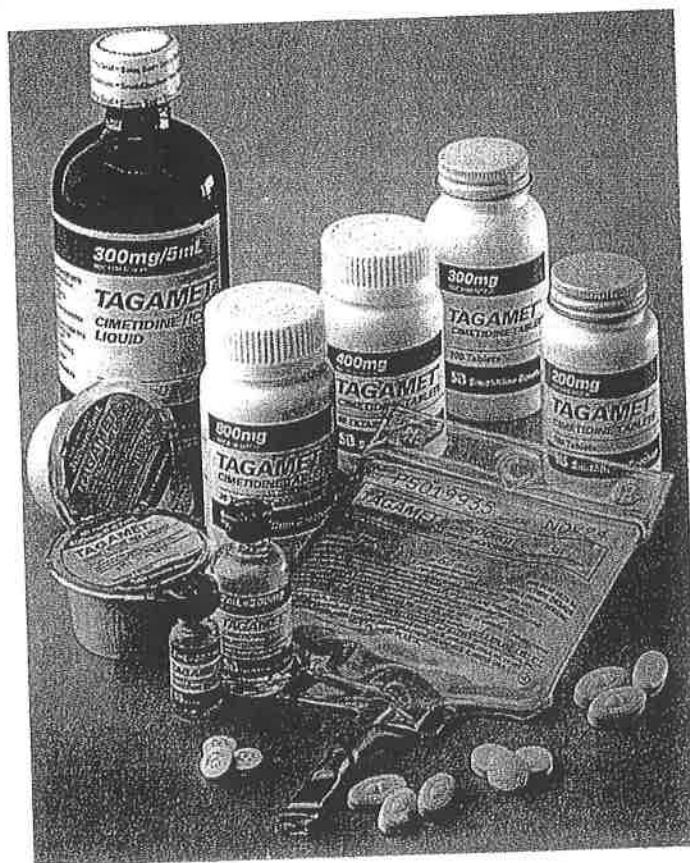

Fig. 3.1 *Examples of varied dosage forms of a drug substance marketed by a pharmaceutical manufacturer to meet the special requirements of the patient. (Courtesy of SmithKline Beecham)*

matters as: the nature of the illness, the manner in which it is treated (locally or through systemic action), and the age and anticipated condition of the patient.

If the medication is intended for systemic use and oral administration is desired, tablets and/or capsules are usually prepared. These dosage units are easily handled by the patient and are most convenient in the self-administration of medication. If a drug substance has application in an emergency situation in which the patient may be comatose or unable to take oral medication, an injectable form of the medication may also be prepared. Many other examples of therapeutic situations affecting dosage form design could be cited, including the preparation of agents for motion sickness, nausea, and vomiting into tablets and skin patches for prevention and suppositories and injections for treatment.

The age of the intended patient also plays a role in dosage form design. For infants and children younger than 5 years of age, pharmaceutical liquids rather than solid dosage forms are preferred for oral administration. These liquids, which are flavored aqueous solutions, syrups or suspensions, are usually administered directly into the infant's or child's mouth by drop, spoon, or oral dispenser (Fig. 3.2) or incorporated into the child's food. A single liquid pediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered. When an infant is in the throes of a vomiting crisis, is gagging, has a productive cough, or is simply rebellious, there may be some question as to how much of the medicine administered is actually swallowed and how much is expectorated. In such instances, injections may be required. Infant size rectal suppositories may also be employed although drug absorption from the rectum is often erratic.

During childhood and even in adult years, a person may have difficulty swallowing solid dosage forms, especially uncoated tablets. For this reason, some medications are formulated as chewable tablets that can be broken up in the mouth before swallowing. Many of these tablets are comparable in texture to an after-dinner mint and break down into a pleasant tasting, creamy material. New, rapidly-disintegrating/dissolving tablets are available that dissolve in the mouth in about 10–15 seconds; this allows the patient to take a tablet but actually swallow a liquid. Capsules have been found by many to be more easily swallowed than whole tablets. If a capsule is allowed to become moist in the mouth before swallowing, it becomes slippery and slides down the throat more readily with a glass of water. Also, a teaspoonful of gelatin dessert or syrup placed in the mouth and partially swallowed before placing the solid dosage form in the mouth aids in swallowing them. Also, in instances in which a person has difficulty swallowing a capsule, the contents may be emptied into a spoon, mixed with jam, honey, or other similar food to mask the taste of the medication and swallowed. Medications intended for the elderly are commonly formulated into oral liquids or may be extemporaneously prepared into an oral liquid by the pharmacist. However, certain tablets and capsules that are designed to have controlled release features should not be crushed or chewed to maintain their integrity and intended performance.

Many patients, particularly the elderly, take multiple medications daily. The more distinctive the size, shape, and color of solid dosage forms, the easier is the proper identification of the medications. Frequent errors in taking medications among the elderly occur because of their multiple drug therapy and reduced eyesight. Dosage forms that allow reduced frequency of administration without sacrifice of efficiency are particularly advantageous.

In dealing with the problem of formulating a drug substance into a proper dosage form, research pharmacists employ knowledge that has been gained through experience with other chemically similar drugs and through the proper utilization of the disciplines of the physical, chemical, and biologic and pharmaceutical sciences. The early stages of any new formulation involves studies to collect basic information on the physical and chemical characteristics of the drug substance to be prepared

Fig. 3.2 *"Pee Dee Dose" brand of oral liquid dispenser used to administer measured volumes of liquid medication to youngsters. (Courtesy of Baxa Corporation)*

into pharmaceutical dosage forms. These basic studies comprise the *preformulation* work needed before actual product formulation begins.

Preformulation Studies

Before the formulation of a drug substance into a dosage form, it is essential that it be chemically and physically characterized. The following *preformulation studies* (1), and others, provide the type of information needed to define the nature of the drug substance. This information then provides the framework for the drug's combination with pharmaceutic ingredients in the fabrication of a dosage form.

Physical Description

It is important to have an understanding of the physical description of a drug substance prior to dosage form development. The majority of drug substances in use today occur as solid materials. Most of them are pure chemical compounds of either crystalline or amorphous constitution. The purity of the chemical substance is essential for its identification as well as for the evaluation of its chemical, physical, and biologic properties. Chemical properties include structure, form and reactivity. Physical properties include such characteristics as its physical description, particle size, crystalline structure, melting point and solubility. Biologic properties relate to its ability to get to a site of action and elicit a biologic response.

Drugs can be used therapeutically as solids, liquids and gases. Liquid drugs are used to a much lesser extent than solid drugs; gases, even less frequently.

Liquid drugs pose an interesting problem in the design of dosage forms or drug delivery systems. Many of the liquids are volatile substances and as such must be physically sealed from the atmosphere to prevent their loss. Amyl nitrite, for example, is a clear yellowish liquid that is volatile even at low temperatures and is also highly flammable. It is maintained for medicinal purposes in small sealed glass cylinders wrapped with gauze or another suitable material. When amyl nitrite is administered, the glass is broken between the fingertips, and the liquid wets the gauze covering, producing vapors that are inhaled by the patient requiring vasodilation. Propylhexedrine provides another example of a volatile liquid drug that must be contained in a closed system to maintain its presence. This drug is used as a nasal inhalant for its vasoconstrictor action. A cylindrical roll of fibrous material is impregnated with propylhexedrine, and the saturated cylinder is placed in a suitable, usually plastic, sealed nasal inhaler. The inhaler's cap must be securely tightened each time it is used. Even then, the inhaler maintains its effectiveness for only a limited period of time due to the volatilization of the drug.

Another problem associated with liquid drugs is that those intended for oral administration cannot generally be formulated into tablet form, the most popular form of oral medication, without undertaking chemical modification of the drug. An exception to this is the liquid drug nitroglycerin, which is formulated into sublingual tablets that disintegrate within seconds after placement under the tongue. However, because the drug is volatile, it has a tendency to escape from the tablets during storage and it is critical that the tablets be stored in tightly sealed glass containers. For the most part, when a liquid drug is to be administered orally and a solid dosage form is desired, two approaches are used. First, the liquid substance may be sealed in a soft gelatin capsule. Clofibrate (Atromid S), vitamins A, D and E, and ethchlorvynol (Placidyl) are examples of liquid drugs commercially available in capsule form. Secondly, the liquid drug may be developed into a solid ester or salt form that will be suitable for tableting or drug encapsulating. For instance, scopolamine hydrobromide is a solid salt of the liquid drug scopolamine and is easily produced into tablets. Another approach to formulate liquids into solids is by mixing the drug with a solid or a melted semisolid material, such as a high molecular weight polyethylene glycol. The melted mixture is poured into hard gelatin capsules where it will harden, and the capsules sealed.

For certain liquid drugs, especially those employed orally in large doses or applied topically, their liquid nature may be of some advantage in therapy. For example, 15-mL doses of mineral oil may be administered conveniently as such. Also, the liquid nature of undecylenic acid certainly does not hinder but rather enhances its use topically in the treatment of fungus infections of the skin. However, for the most part, solid materials are preferred by pharmacists in formulation work because of their ease of preparation into tablets and capsules.

Formulation and stability difficulties arise less frequently with solid dosage forms than with liquid pharmaceutical preparations, and for this reason many new drugs first reach the market as tablets or dry-filled capsules. Later, when the pharmaceutical problems are resolved, a liquid form of the same drug may be marketed. This procedure, when practiced, is doubly advantageous, because for the most part physicians and patients alike prefer small, gen-

erally tasteless, accurately dosed tablets or capsules to the analogous liquid forms. Therefore, marketing a drug in solid form first is more practical for the manufacturer and also suits the majority of patients. It is estimated that tablets and capsules comprise the dosage form dispensed 70% of the time by community pharmacists, with tablets dispensed twice as frequently as capsules.

Microscopic Examination

Microscopic examination of the raw drug substance is an important step in preformulation work.

It gives an indication of particle size and particle size range of the raw material as well as the crystal structure. Photomicrographs of the initial and subsequent batch lots of the drug substance can provide important information should problems arise in formulation processing attributable to changes in particle or crystal characteristics of the drug. During some processing procedures, the solid drug powders must flow freely and not become entangled. Spherical and oval-shaped powders flow more easily than needle-shaped powders and make processing easier.

Physical Pharmacy Capsule 3.1   Melting Point Depression

The *melting point,* or *freezing point,* of a pure crystalline solid is defined as that temperature where the pure liquid and solid exist in equilibrium. Low melting point drugs may soften during a processing step where heat is generated, such as particle size reduction, compression, sintering, etc. Also, the melting point/range of a drug can be used as an indicator of purity of chemical substances (a pure substance would ordinarily be characterized by a very sharp melting peak). An altered peak or a peak at a different temperature may be indicative of an adulterated or impure drug. This is explained as follows.

The *latent heat of fusion* is the quantity of heat absorbed when 1 g of a solid melts; the molar heat of fusion (ΔH_f) is the quantity of heat absorbed when 1 mole of a solid melts. High-melting-point substances have high heats of fusion and low-melting-point substances have low heats of fusion. These characteristics are related to the types of bonding in the specific substance. For example, ionic materials have high heats of fusion (NaCl melts at 801°C with a heat of fusion of 124 cal/G) and those with weaker van der Waals forces have low heats of fusion (paraffin melts at 52°C with a heat of fusion of 35.1 cal/g). Ice, with weaker hydrogen bonding, has a melting point of 0°C and a heat of fusion of 80 cal/G.

The addition of a second component to a pure compound (A), resulting in a mixture, will result in a melting point that is lower than that of the pure compound. The degree to which the melting point is lowered is proportional to the mole fraction (N_A) of the second component that is added. This can be expressed as:

$$\Delta T = \frac{2.303\ RTT_0}{\Delta H_f}\ \log N_A$$

where ΔH_F is the molar heat of fusion,
  T is the absolute equilibrium temperature,
  T_0 is the melting point of pure A, and
  R is the gas constant.

Two things are noteworthy in contributing to the extent of melting-point lowering.

1. Evident from this relationship is the inverse proportion between the melting point and the heat of fusion. When a second ingredient is added to a compound with a low molar heat of fusion, a large lowering of the melting point is observed; substances with a high molar heat of fusion will show little change in melting point with the addition of a second component.
2. The extent of lowering of the melting point is also related to the melting point itself. Compounds with low melting points are affected to a greater extent than compounds with high melting points upon the addition of a second component (i.e., low-melting-point compounds will result in a greater lowering of the melting point than those with high melting points).

Melting Point Depression

A characteristic of a pure substance is a defined melting point or melting range. If not pure, the substance will exhibit a depressed melting point. This phenomenon is commonly used to determine the purity of a drug substnce and; in some cases, the compatibility of various substances before inclusion in the same dosage form. This characteristic is further described in the physical pharmacy capsule entitled"Melting Point Depression."

The Phase Rule

Phase diagrams are often constructed to provide a visual picture of the existence and extent of the presence of solid and liquid phases in binary, ternary and other mixtures. Phase diagrams are normally two-component (binary) representations as shown in the physical pharmacy capsule"The Phase Rule," but multicomponent phase diagrams can also be constructed.

Particle Size

Certain physical and chemical properties of drug substances are affected by the particle size distribution, including drug dissolution rate, bioavailability, content uniformity, taste, texture, color, and stability. In addition, properties such as flow characteristics and sedimentation rates, among others, are also important factors related to particle size. It is essential to establish as early as possible how the particle size of the drug substance may affect formulation and product efficacy. Of special interest is the effect of particle size on the drug's absorption. Particle size significantly influences the oral absorption profiles of certain drugs as griseofulvin, nitrofurantoin, spironolactone, and procaine penicillin. Also, satisfactory content uniformity in solid dosage forms depends to a large degree on particle size and the equal distribution of the active ingredient throughout the formulation. Particle size is discussed further in Chapters 4 and 6.

Polymorphism

An important factor on formulation is the crystal or amorphous form of the drug substance. Polymorphic forms usually exhibit different physical-chemical properties including melting point and solubility. The occurrence of polymorphic forms with drugs is relatively common and it has been estimated that polymorphism is exhibited by at least one-third of all organic compounds.

In addition to the polymorphic forms in which compounds may exist, they also can occur in non-crystalline or amorphous forms. The energy required for a molecule of drug to escape from a crys-tal is much greater than required to escape from an amorphous powder. Therefore, the amorphous form of a compound is always more soluble than a corresponding crystal form.

Evaluation of crystal structure, polymorphism, and solvate form is an important preformulation activity. The changes in crystal characteristics can influence bioavailability, chemical and physical stability, and have important implications in dosage form process functions. For example, it can be a significant factor relating to the tableting processes due to flow and compaction behaviors, among others. Various techniques are used in determining crystal properties. The most widely used methods are hot stage microscopy, thermal analysis, infrared spectroscopy, and x-ray diffraction.

Solubility

An important physical–chemical property of a drug substance is solubility, especially aqueous system solubility. A drug must possess some aqueous solubility for therapeutic efficacy. For a drug to enter the systemic circulation to exert a therapeutic effect, it must first be in solution. Relatively insoluble compounds often exhibit incomplete or erratic absorption. If the solubility of the drug substance is less than desirable, consideration must be given to improve its solubility. The methods to accomplish this will depend on the chemical nature of the drug and the type of drug product under consideration. The chemical modification of the drug into salt or ester forms is a technique frequently used to obtain more soluble compounds.

A drug's solubility is usually determined by the equilibrium solubility method, by which an excess of the drug is placed in a solvent and shaken at a constant temperature over a prolonged period of time until equilibrium is obtained. Chemical analysis of the drug content in solution is performed to determine degree of solubility.

Solubility and Particle Size

Although solubility is normally considered a physicochemical constant, small increases in solubility can be accomplished by particle size reduction as described in the physical pharmacy capsule, "Solubility and Particle Size."

Solubility and pH

Another technique, if the drug is to be formulated into a liquid product, involves the adjustment of the pH of the solvent in which the drug is to be dissolved to enhance solubility. However, there are many drug substances for which pH adjustment is not an effective means of improving solubility.

Physical Pharmacy Capsule 3.2   **The Phase Rule**

A phase diagram, or temperature-composition diagram, represents the melting point as a function of composition of two or three component systems. The figure is an example of such a representation for a two-component mixture. This phase diagram is of a two-component mixture in which the components are completely miscible in the molten state and no solid solution or addition compound is formed in the solid state. As is evident, starting from the extremes of either pure component A or pure component B, as the second component is added, the melting point of the pure component decreases. There is a point on this phase diagram at which a minimum melting point occurs (i.e., the eutectic point). As is evident, there are four regions, or phases, in this diagram, representing the following:
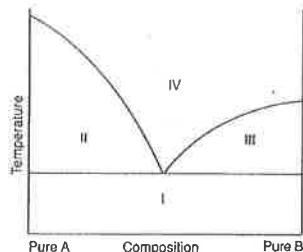
I.   Solid A + Solid B
II. Solid A + Melt
III. Solid B + Melt
IV. Melt

Each phase is a homogenous part of the system, physically separated by distinct boundaries.
A description of the conditions under which these phases can exist is called the *Phase Rule,* which can be presented as:

$$F = C - P + X$$

where F is the number of degrees of freedom,
    C is the number of components,
    P is the number of phases, and

X is a variable dependent upon selected considerations of the phase diagram (1,2 or 3).

"C" describes the minimum number of chemical components that need to be specified to define the phases present. The F is the number of independent variables that must be specified to define the complete system (e.g., temperature, pressure, concentration).

EXAMPLE 1

In a mixture of menthol and thymol, a phase diagram similar to that illustrated can be obtained. To describe the number of degrees of freedom in the part of the graph moving from the curved line starting at pure A, progressing downward to the eutectic point, and then following an increasing melting point to pure B, it is evident from this presentation that either temperature or composition will describe this system, since it is assumed in this instance that pressure is constant. Therefore, the number of degrees of freedom to describe this portion of the phase diagram is given by:

$$F = 2 - 2 + 1 = 1$$

In other words, along this line, either temperature or composition will describe the system.

EXAMPLE 2

When in the area of a single phase of the diagram, such as the melt (IV), the system can be described as:

$$F = 2 - 1 + 1 = 2$$

In this portion of the phase diagram, two factors, temperature and composition, can be varied without a change in the number of phases in the system.

EXAMPLE 3

At the eutectic point,

$$F = 2 - 3 + 1 = 0$$

and any change in the concentration or temperature may cause a disappearance of one of the two solid phases or the liquid phase.

Phase diagrams are valuable in interpreting interactions between two or more components, relating not only to melting point depression and possible liquefaction at room temperature but also the formation of solid solutions, coprecipitates, and other solid-state interactions.

Physical Pharmacy Capsule 3.3   **Solubility and Particle Size**

The particle size and surface area of a drug exposed to a medium can affect actual solubility, within reason. For example, in the following relationship:

$$\log \frac{S}{S_0} = \frac{2\gamma V}{2.303\ RTr}$$

where S is the solubility of the small particles,
     S_0 is the solubility of the large particles,
     γ is the surface tension
     V is the molar volume
     R is the gas constant
     T is the absolute temperature
     r is the radius of the small particles.

The equation can be used to estimate the decrease in particle size required to result in an increase in solubility. For example, for a desired increase in solubility of 5%, this would require an increase in the S/So ratio to 1.05, that is, the left term in the equation would become "log 1.05." If an example is used for a powder with a surface tension of 125 dynes/cm, the molar volume is 45 cm³ and the temperature is 27°C, what is the particle size required to obtain the 5% increase in solubility?

$$\log 1.05 = \frac{(2)(125)(45)}{(2.303)(8.314 \times 10^7)(300)r}$$

$$r = 9.238 \times 10^{-6}\ cm\ or\ 0.09238\mu$$

A number of factors are involved in actual solubility enhancement and this is only a basic introduction of the general effects of particle size reduction.

Weak acidic or basic drugs may require extremes in pH that are outside accepted physiologic limits or may cause stability problems with formulation ingredients. Adjustment of pH usually has little effect on the solubility of non-electrolytes. In many cases, it is desirable to utilize co-solvents or other techniques such as complexation, micronization, or solid dispersion to improve aqueous solubility. The effect of pH on solubility is illustrated in the physical pharmacy capsule "Solubility and pH."

In recent years, more and more physicochemical information on drugs is being made available to pharmacists in routinely used reference books. This type of information is important for pharmacists in different types of practice, especially those involved in compounding and pharmacokinetic monitoring.

Dissolution

Variations in the biological activity of a drug substance may be brought about by the rate at which it becomes available to the organism. In many instances, dissolution rate, or the time it takes for the drug to dissolve in the fluids at the absorption site, is the rate-limiting step in the absorption process. This is true for drugs administered orally in solid forms such as tablets, capsules or suspensions, as well as drugs administered intramuscularly in the form of pellets or suspensions. When the dissolution rate is the rate-limiting step, anything which affects it will also affect absorption. Consequently, dissolution rate can affect the onset, intensity, and duration of response, and control the overall bioavailability of the drug from the dosage form, as discussed in the previous chapter.

The dissolution rate of drugs may be increased by decreasing the drug's particle size. It may also be increased by increasing its solubility in the diffusion layer. The most effective means of obtaining higher dissolution rates is to use a highly water soluble salt of the parent substance. Although a soluble salt of a weak acid will subsequently precipitate as the free acid in the bulk phase of an acidic solution, such as gastric fluid, it will do so in the form of fine particles with a large surface area.

The dissolution rates of chemical compounds are determined by two methods: the constant surface

Physical Pharmacy Capsule 3.4   **Solubility and pH**

pH is one of the most important factors involved in the formulation process. Two areas of critical importance are the effects of pH on solubility and stability. The effect of pH on solubility is critical in the formulation of liquid dosage forms, from oral and topical solutions to intravenous solutions and admixtures.

The solubility of a weak acid or base is often pH dependent. The total quantity of a monoprotic weak acid (HA) in solution at a specific pH is the sum of the concentrations of both the free acid and salt (A^-) forms. If excess drug is present, the quantity of free acid in solution is maximized and constant due to its saturation solubility. As the pH of the solution is increased, the quantity of drug in solution increases because the water-soluble ionizable salt is formed. The expression is:

$$HA \xrightarrow{\;\;K_a\;\;} H^+ + A^-$$
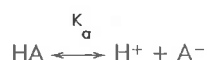
where K_a is the dissociation constant.

There may be a certain pH level reached where the total solubility (S_T) of the drug solution is saturated with respect to both the salt and acid forms of the drug, i.e., the pH_{max}. The solution can be saturated with respect to the salt at pH values higher than this, but not with respect to the acid. Also, at pH values less than this, the solution can be saturated with respect to the acid, but not to the salt. This is illustrated in the accompanying figure.

To calculate the total quantity of drug that can be maintained in solution at a selected pH, two different equations can be used, depending on whether the product is to be in a pH region above or below the pH_{max}. The following equation is used when below the pH_{max}:

$$S_T = S_a \left(1 + \frac{K_a}{[H^+]} \right) \qquad\qquad \text{(Equation 1)}$$

The next equation is used when above the pH_{max}:

$$S_T = S'_A \left(1 + \frac{[H^+]}{K_a} \right) \qquad\qquad \text{(Equation 2)}$$

where S_a is the saturation solubility of the free acid, and

$S'a$ is the saturation solubility of the salt form.

EXAMPLE

A pharmacist prepares a 3.0% solution of an antibiotic as an ophthalmic solution and dispenses it to a patient. A few days later the patient returns the eye drops to the pharmacist because the product contains a precipitate. The pharmacist, checking the pH of the solution and finding it to be 6.0, reasons that the problem might be pH-related. The physicochemical information of interest on the antibiotic includes the following:

Molecular weight	285 (salt) 263 (free acid)
3.0% solution of the drug is a	0.1053 molar solution
Acid form solubility (S_a)	3.1 mg/mL (0.0118 molar)
K_a	5.86×10^{-6}

Using Equation 1, the pharmacist calculates the quantity of the antibiotic that would be in solution at a pH of 6.0 (Note: pH of 6.0 = [H+] of 1×10^{-6})

$$S_T = 0.0118 \left[1 + \frac{5.86 \times 10^{-6}}{1 \times 10^{-6}} \right] = 0.0809 \text{ molar}$$

Solubility and pH (Continued)

From this the pharmacist knows that, at a pH of 6.0, a 0.0809 molar solution could be prepared. However, the concentration that was to be prepared was a 0.1053 molar solution; consequently, the drug will not be in solution at that pH. What may have occurred was the pH was all right initially but shifted to a lower pH after a period of time, resulting in precipitation of the drug. The question is then asked, At what pH (hydrogen ion concentration) will the drug remain in solution? This can be calculated using the same equation and the information that is available. The S_T value is 0.1053 molar.

$$0.1053 = 0.0118 \left[1 + \frac{5.86 \times 10^{-6}}{[H^+]}\right]$$

$$[H^+] = 7.333 \times 10^{-7}, \text{ or a pH of } 6.135$$

The pharmacist then prepares a solution of the antibiotic, adjusting the pH to greater than about 6.2 using a suitable buffer system, and dispenses the solution to the patient—with positive results.

An interesting phenomenon can be discussed briefly concerning the close relationship of pH to solubility. At a pH of 6.0, only a 0.0809 molar solution could be prepared, but at a pH of 6.13 a 0.1053 molar solution could be prepared. In other words, a difference of 0.13 pH units resulted in:

$$\frac{0.1053 - 0.0809}{0.0809} = 30.1\% \text{ more drug going into solution at the higher pH}$$
$$\text{compared to the lower pH}$$

In other words, a very small change in pH resulted in about 30% more drug going into solution. According to the figure, the slope of the curve would be very steep for this example drug and a small change in pH (x-axis) results in a large change in solubility (y-axis). From this, it can be reasoned that if one observes the pH:solubility profile of a drug, it is possible to predict the magnitude of the pH change on its solubility.

In recent years, it has been interesting to not that more and more physiochemical information on drugs is being made available to pharmacists in routinely used reference books. This type of information is important for pharmacists in different types of practice, especially those involved in compounding and pharmacokinetic monitoring.
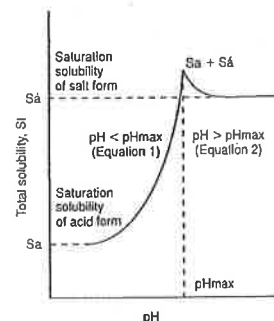
method which provides the intrinsic dissolution rate of the agent, and particulate dissolution in which a suspension of the agent is added to a fixed amount of solvent without exact control of surface area.

The constant surface method utilizes a compressed disc of known area. This method eliminates surface area and surface electrical charges as dissolution variables. The dissolution rate obtained by this method is termed the *intrinsic dissolution rate,* and is characteristic of each solid compound and a given solvent under the fixed experimental conditions. The value is expressed as milligrams dissolved per minute centimeters squared (mg/min/cm²). It has been suggested that this value is useful in predicting probable absorption problems due to dissolution rate. In particulate dissolution, a weighed amount of powdered sample is added to the dissolution medium in a constant agitation system. This method is frequently used to study the influence of particle size, surface area, and excipients upon the active agent. Occasionally, an inverse relationship of particle size to dissolution is noted due to the surface properties of the drug. In these instances, surface charge and/or agglomeration results in the reduced particle size form of the drug presenting a lower effective surface area to the solvent due to incomplete wetting or agglomeration. Fick's Laws describe the relationship of diffusion and dissolution of the active drug in the dosage form and when administered in the body, as shown in the physical pharmacy capsule entitled Fick's Laws of Diffusion and the Noyes-Whitney Equation.

Early formulation studies should include the

Physical Pharmacy Capsule 3.5   **Fick's Laws of Diffusion and the Noyes-Whitney Equation**

All drugs must diffuse through various barriers when administered to the body. For example, some drugs must diffuse through the skin, gastric mucosa or some other barrier to gain access to the interior of the body. Parenterally administered drugs must diffuse through muscle, connective tissue, etc. to get to the site of action; even intravenous drugs must diffuse from the blood to the site of action. Drugs must also diffuse through various barriers for metabolism and excretion.

Considering all the diffusion processes that occur in the body (passive, active and facilitated), it is not surprising that the laws governing diffusion are very important in designing drug delivery systems. In fact, diffusion is important not only in the body but also in some quality control procedures used to determine batch-to-batch uniformity of products (dissolution test for tablets based on the Noyes-Whitney equation, which can be derived from Fick's law).

When individual molecules move within a substance, diffusion is said to occur. This may occur as the result of a concentration gradient or by random molecular motion.

Probably the most widely used laws of diffusion are known as Fick's laws; the first and second laws. Fick's First Law involving steady-state diffusion (where dc/dx does not change) is derived from the following expression for the quantity of material (M) flowing through a cross-section of a barrier (S) in unit time (t) expressed as the flux (J);

$$J = dM/(S\ dt)$$

Under a concentration gradient (dc/dx), Fick's First Law can be expressed as:

$$J = D[(C_1 - C_2/h]\ \text{or}\ J = -D\ (dC/dx)$$

where J is the flux of a component across a plane of unit area, C_1 and C_2 are the concentrations in the donor and receptor compartments, h is the membrane thickness and D is the diffusion coefficient (or diffusivity). The sign is negative denoting that the flux is in the direction of decreasing concentration. The units of J are $g/(cm^2\ s)$, C is in g/cm^3, M in grams or moles, S in cm^2, x in cm and the units of D would be in cm^2/s.

"D" is appropriately called a diffusion coefficient, not a diffusion constant, as it is subject to change. "D", the diffusion coefficient, may actually change in value with increased concentrations. Also, "D" can be affected by temperature, pressure, solvent properties and the chemical nature of the drug itself. To study the rate of change of the drug in the system, one needs an expression that relates the change in concentration with time at a definite location in place of the mass of drug diffusing across a unit area of barrier in unit time; this expression is known as Fick's Second Law. This law can be summarized as it states that the change in concentration in a particular place with time is proportional to the change in concentration gradient at that particular place in the system.

In summary, Fick's First Law relates to a steady state flow whereas Fick's Second Law relates to a change in concentration of drug with time, at any distance, or a nonsteady state of flow.

The diffusion coefficients ($D \times 10^6$) of various compounds in water (25°C) and other media have been determined as follows: ethanol, 12.5 cm^2/sec; glycine, 10.6 cm^2/sec; sodium lauryl sulfate, 6.2 cm^2/sec; glucose, 6.8 cm^2/sec.

The concentration of drug in the membrane can be calculated using the partition coefficient (K) and the concentration in the donor and receptor compartments.

$$K = C_1/C_d = C_2/C_r$$

where C_1 and C_d are the concentrations in the donor compartment (g/cm^3) and C_2 and C_r are the concentrations in the receptor compartment (g/cm^3).

K is the partition coefficient of the drug between the solution and the membrane. It can be estimated using the oil solubility of the drug vs. the water solubility of the drug. Usually, the higher the partition coefficient, the more the drug will be soluble in a lipophilic substance. We can now write the expression:

$$dM/dt = [DSK(C_d - C_r)]/h$$

Fick's Laws of Diffusion and the Noyes-Whitney Equation   (Continued)

or, in sink conditions,

$$dM/dt = DSKC_d/h = PSC_d$$

The permeability coefficient (cm/sec) can be obtained by rearranging to:

$$P = DK/h$$

EXAMPLE 1

A drug passing through a 1 mm thick membrane has a diffusion coefficient of 4.23×10^{-7} cm^2/sec, and an o/w partition coefficient of 2.03. The radius of the area exposed to the solution is 2 cm, and the concentration of the drug in the donor compartment is 0.5 mg/mL. Calculate the permeability and the diffusion rate of the drug.

$$h = 1 \text{ mm} = 0.1 \text{ cm}$$
$$D = 4.23 \times 10^{-7} \text{ cm}^2/\text{sec}$$
$$K = 2.03$$
$$r = 2 \text{ cm}, S = \pi(2\text{cm})^2 = 12.57 \text{ cm}^2$$
$$Cd = 0.5 \text{ mg/mL}$$
$$P = [(4.23 \times 10^{-7} \text{ cm}^2/\text{sec})\ (2.03)]/0.1 \text{ cm} = 8.59 \times 10^{-6} \text{ cm/sec}$$
$$dM/dt = (8.59 \times 10^{-6} \text{ cm/sec})\ (12.57 \text{ cm}^2)(0.5 \text{ mg/mL}) = 5.40 \times 10^{-5} \text{ mg/sec}$$
$$(5.40 \times 10^{-5} \text{ mg/sec})(3600 \text{ sec/hr}) = 0.19 \text{ mg/hr}$$

In the dissolution of particles of drug, the dissolved molecules diffuse away from the individual particle body. An expression to describe this was derived from Fick's equations and is known as the Noyes and Whitney expression, proposed in 1897. It can be written as follows:

$$dC/dt = (DS/Vh)(Cs - C)$$

where C is the concentration of drug dissolved at time t, D is the diffusion coefficient of the solute in solution, S is the surface area of the exposed solid, V is the volume of solution, h is the thickness of the diffusion layer, Cs is the saturation solubility of the drug and C is the concentration of solute in the bulk phase at a specific time, t. It is common practice to utilize sink conditions where C does not exceed about 20% of the solubility of the drug being investigated. Under these conditions, the expression simplifies to:

$$dC/dt = DSCs/Vh$$

and incorporating the volume of solution (V), the thickness of the diffusion layer (h) and the diffusivity coefficient (D) into a coefficient k (to take into account the various factors in the system), the expression becomes:

$$dC/dt = kSCs$$

As the factors are held constant, it becomes apparent that the dissolution rate of a drug can be proportional to the surface area exposed to the dissolution media. A number of other expressions have been derived for specific application to various situations and conditions.

It should be obvious to the reader that these relationships expressed as Fick's First and Second Laws and the Noyes-Whitney equation have great importance and relevance in pharmaceutical systems.

EXAMPLE 2

The following data was obtained using the USP 23/NF dissolution apparatus I. The drug is soluble 1 gram in 3 mL of water so sink conditions were maintained, the surface area of the tablet exposed was 1.5 cm^2 (obtained by placing the tablet in a special holder exposing only one side to the dissolution media) and the dosage form studied involved a 16 mg sustained release tablet; the release pattern should be zero order. What is the rate of release of drug?

Fick's Laws of Diffusion and the
Noyes-Whitney Equation   (Continued)

Time (hr)	Drug concentration (mg/900 mL of solution)	Graph of Release Profile
0	0	
0.5	1	
1.0	1.9	
2.0	4.1	
4.0	8.0	
6 0	11.8	
8.0	15.9	

In this problem, since the surface area (S) was maintained constant at 1.5 cm^2 and the solubility (Cs) of the drug is constant at 1 g in 3 mL of water, then the plot of concentration (C) versus time (t) would yield a slope with a value of "kSCs", or "k$_2$", expressing the rate of release of the drug.

$$dC/dt = kSCs$$

the slope of the line would be $= \Delta y/\Delta x = (y_2 - y_1)/(x_2 - x_1)$

$$= (15.9 \text{ mg} - 0 \text{ mg})/(8.0 \text{ h} - 0 \text{ h})$$

$$= 15.9/8 = 1.99 \text{ mg/h}$$

Therefore, the rate of release of the sustained release preparation is 1.99 or approximately 2 mg per hour. From this, the quantity of drug released at any time (t) can be calculated.

effects of pharmaceutic ingredients on the dissolution characteristics of the drug substance.

Membrane Permeability

Modern preformulation studies include an early assessment of passage of drug molecules across biological membranes. To produce a biological response, the drug molecule must first cross a biological membrane. The biological membrane acts as a lipid barrier to most drugs and permits the absorption of lipid soluble substances by passive diffusion while lipid insoluble substances can diffuse across the barrier only with considerable difficulty, if at all. The interrelationship of the dissociation constant, lipid solubility, and pH at the absorption site and absorption characteristics of various drugs are the basis of the pH-partition theory.

Data obtained from the basic physicochemical studies, specifically, pKa, solubility, and dissolution rate provide an indication of absorption expectations. To enhance these data, a technique using the "everted intestinal sac" may be used in evaluating absorption characteristics of drug substances. In this method, a piece of intestine is removed from an intact animal, everted, filled with a solution of the drug substance, and the degree and rate of passage of the drug through the membrane sac is determined. Through this method, both passive and active transport can be evaluated.

In the latter stages of preformulation testing or early formulation studies, animals and man must be studied to assess the absorption efficiency, pharmacokinetic parameters and to establish possible *in vitro/in vivo* correlation for dissolution and bioavailability.

Partition Coefficient

The use of the partition coefficient is described in some detail in the physical pharmacy capsule entitled "Partition Coefficient."

Inherent in this procedure is the selection of appropriate extraction solvents, drug stability, use of salting-out additives, and environmental concerns.

In formulation development, the octanol-water partition coefficient is commonly used. Following the illustrations provided above, it is defined as:

$$P = \frac{(\text{Conc. of drug in octanol})}{(\text{Conc. of drug in water})}$$

P is dependent on the drug concentration only if the drug molecules have a tendency to associate in

Physical Pharmacy Capsule 3.6   **Partition Coefficient**

The oil/water partition coefficient is a measure of a molecule's lipophilic character; that is, its preference for the hydrophilic or lipophilic phase. If a solute is added to a mixture of two immiscible liquids, it will distribute between the two phases and reach an equilibrium at a constant temperature. The distribution of the solute (unaggregated and undissociated) between the two immiscible layers can be described as:

$$K = C_U/C_L$$

where K is the distribution constant or partition constant,
       C_U is the concentration of the drug in the upper phase, and
       C_L is the concentration of the drug in the lower phase.

This information can be effectively used in the:

1. Extraction of crude drugs,
2. Recovery of antibiotics from fermentation broths,
3. Recovery of biotechnology-derived drugs from bacterial cultures,
4. Extraction of drugs from biologic fluids for therapeutic drug monitoring,
5. Absorption of drugs from dosage forms (ointments, suppositories, transdermal patches),
6. Study of the distribution of flavoring oil between oil and water phases of emulsions, and
7. In other applications.

The basic relationship given above can be used to calculate the quantity of drug extracted from, or remaining behind in, a given layer and to calculate the number of extractions required to remove a drug from a mixture.

The concentration of drug found in the upper layer (U) of two immiscible layers is given by:

$$U = Kr/(Kr + 1)$$

where K is the distribution partition constant, and
       r is V_u/V_l, or the ratio of the volume of upper and lower phases.

The concentration of drug remaining in the lower layer (L) is given by:

$$L = 1/(Kr + 1)$$

If the lower phase is successively re-extracted with n equal volumes of the upper layer, each upper (U_n) contains the following fraction of the drug:

$$U_n = Kr/(Kr + 1)^n$$

where U_n is the fraction contained in the nth extraction, and
       n is the nth successive volume.

The fraction of solute remaining in the lower layer (L_n) is given by:

$$L_n = 1/(kr + 1)^n$$

More efficient extractions are obtained using successive small volumes of the extraction solvent (as compared to single larger volumes). This can be calculated as follows when the same volume of extracting solvent is used, but in divided portions. For example, the fraction L_n remaining after the nth extraction is given by:

$$L_n = \frac{1}{\left(\dfrac{Kr}{n}+1\right)^n}$$

EXAMPLE 1
At 25°C and at pH 6.8, the K for a second generation cephalosporin is 0.7 between equal volumes of butanol and the fermentation broth. Calculate the U, L, and L_n (using the same volume divided into fourths).

Partition Coefficient (Continued)

$$U = 0.7/(0.7 + 1) = 0.41 \text{ The fraction of drug extracted into the upper layer}$$
$$L = 1/(0.7 + 1) = 0.59 \text{ The fraction of drug remaining in the lower layer}$$

The total of the fractions in the U and L = 0.41 + 0.59 = 1.

If the fermentation broth is extracted with four successive extractions accomplished by dividing the quantity of butanol used into fourths, the quantity of drug remaining after the fourth extraction is

$$L_{4th} = \frac{1}{\left(\dfrac{0.7 \times 1}{4} + 1\right)^4} = 0.525$$

From this, the quantity remaining after a single volume, single extraction is 0.59, but when the single volume is divided into fourths and four successive extractions are done, the quantity remaining is 0.525; therefore, more was extracted using divided portions of the extracting solvent.

Inherent in this procedure is the selection of appropriate extraction solvents, drug stability, use of salting-out additives, and environmental concerns.

solution. For an ionizable drug, the following equation is applicable:

$$P = \frac{(\text{Conc. of drug in octanol})}{[1- \alpha](\text{Conc. of drug in water})}$$

where α equals the degree of ionization.

pKa/Dissociation Constants

Among the physicochemical characteristics of interest is the extent of dissociation/ionization of drug substances. This is important because the extent of ionization has an important effect on the formulation and pharmacokinetic parameters of the drug. The extent of dissociation/ionization is, in many cases, highly dependent on the pH of the medium containing the drug. In formulation, often the vehicle is adjusted to a certain pH in order to obtain a certain level of ionization of the drug for solubility and stability purposes. In the pharmacokinetic area, the extent of ionization of a drug is an important affector of its extent of absorption, distribution, and elimination. Dissociation constant or pKa is usually determined by potentiometric titration. For the practicing pharmacist, it is important in predicting precipitation in admixtures and in the calculating of the solubility of drugs at certain pH values. The physical pharmacy capsule on "pKa/Dissociation Constants" presents a brief summary of dissociation/ionization concepts.

Drug and Drug Product Stability

One of the most important activities of preformulation work is the evaluation of the physical and chemical stability of the pure drug substance. It is essential that these initial studies be conducted using drug samples of known purity. The presence of impurities can lead to erroneous conclusions in such evaluations. Stability studies conducted in the preformulation phase include solid state stability of the drug alone, solution phase stability, and stability in the presence of expected excipients. Initial investigation begins through knowledge of the drug's chemical structure which allows the preformulation scientist to anticipate the possible degradation reactions.

Drug Stability: Mechanisms of Degradation

Chemical instability of medicinal agents may take many forms, because the drugs in use today are of such diverse chemical constitution. Chemically, drug substances are alcohols, phenols, aldehydes, ketones, esters, ethers, acids, salts, alkaloids, glycosides, and others, each with reactive chemical groups having different susceptibilities toward chemical instability. Chemically, the most frequently encountered destructive processes are hydrolysis and oxidation.

Hydrolysis is a solvolysis process in which (drug) molecules interact with water molecules to yield breakdown products of different chemical constitution. For example, aspirin or acetylsalicylic acid combines with a water molecule and hydrolyzes into one molecule of salicylic acid and one molecule of acetic acid:

The process of hydrolysis is probably the most important single cause of drug decomposition mainly because a great number of medicinal agents are esters or contain such

Physical Pharmacy Capsule 3.7   pKa/Dissociation Constants

The dissociation of a weak acid in water is given by the expression:

$$HA \leftrightarrow H^+ + A^-$$

$$K_1[HA] \leftrightarrow K_2[H^+][A^-]$$
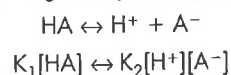
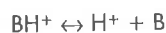At equilibrium, the reaction rate constants K_1 and K_2 are equal. This can be rearranged, and the dissociation constant defined as

$$K_a = \frac{K_1}{K_2} = \frac{[H^+][A^-]}{[HA]}$$

where K_a is the acid dissociation constant.

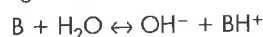For the dissociation of a weak base that does not contain a hydroxyl group, the following relationship can be used:

$$BH^+ \leftrightarrow H^+ + B$$

The dissociation constant is described by:

$$K_a = \frac{[H^+][B]}{[BH^+]}$$

The dissociation of a hydroxyl-containing weak base,

$$B + H_2O \leftrightarrow OH^- + BH^+$$

The dissociation constant is described by:

$$K_b = \frac{[OH^-][BH^+]}{[B]}$$

The hydrogen ion concentrations can be calculated for the solution of a weak acid using:

$$[H^+] = \sqrt{K_a c}$$

Similarly, the hydroxyl ion concentration for a solution of a weak base is approximated by:

$$[OH^-] = \sqrt{K_b c}$$

Some practical applications of these equations are as follows.

EXAMPLE 1
The K_a of lactic acid is 1.387×10^{-4} at 25°C. What is the hydrogen ion concentration of a 0.02 M solution?

$$[H^+] = \sqrt{1.387 \times 10^{-4} \times 0.02} = 1.665 \times 10^{-3} \text{ G-ion/L.}$$

EXAMPLE 2
The K_b of morphine is 7.4×10^{-7}. What is the hydroxyl ion concentration of a 0.02 M solution?

$$[OH] = \sqrt{7.4 \times 10^{-7} \times 0.02} = 1.216 \times 10^{-4} \text{ G-ion/L.}$$

other groupings as substituted amides, lactones, and lactams, which are susceptible to the hydrolytic process (2).

Another destructive process is oxidation. The oxidative process is destructive to many drug types, including aldehydes, alcohols, phenols, sugars, alkaloids, and unsaturated fats and oils. Chemically, oxidation involves the loss of electrons from an atom or a molecule. Each electron lost is accepted by some other atom or molecule, thereby accomplishing the reduction of the recipient. In inorganic chemistry, oxidation is accompanied by an increase in the positive valence of an element—for example, ferrous (+2) oxidizing to ferric (+3). In organic

chemistry, oxidation is frequently considered synonymous with the loss of hydrogen (dehydrogenation) from a molecule. The oxidative process frequently involves free chemical radicals, which are molecules or atoms containing one or more unpaired electrons, as molecular (atmospheric) oxygen ($\bullet O—O\bullet$) and free hydroxyl ($\bullet OH$). These radicals tend to take electrons from other chemicals, thereby oxidizing the donor.

Many of the oxidative changes in pharmaceutical preparations have the character of autoxidations. Autoxidations occur spontaneously under the initial influence of atmospheric oxygen and proceed slowly at first and then more rapidly as the process continues. The process has been described as a type of chain reaction commencing by the union of oxygen with the drug molecule and continuing with a free radical of this oxidized molecule participating in the destruction of other drug molecules and so forth.

In drug product formulation work, steps are taken to reduce or prevent the occurrence of drug substance deterioration due to hydrolysis, oxidation, and other processes. These techniques are discussed later.

Drug and Drug Product Stability: Kinetics and Shelf-Life

Stability is defined as the extent to which a product retains, within specified limits, and throughout its period of storage and use (i.e., its shelf-life), the same properties and characteristics that it possessed at the time of its manufacture.

There are five types of stability of concern to pharmacists:

1. *Chemical.* Each active ingredient retains its chemical integrity and labeled potency, within the specified limits.
2. *Physical.* The original physical properties, including appearance, palatability, uniformity, dissolution and suspendability are retained.
3. *Microbiologic.* Sterility or resistance to microbial growth is retained according to the specified requirements. Antimicrobial agents that are present retain effectiveness within specified limits.
4. *Therapeutic.* The therapeutic effect remains unchanged.
5. *Toxicologic.* No significant increase in toxicity occurs.

Chemical stability is important for selecting storage conditions (temperature, light, humidity), selecting the proper container for dispensing (glass vs. plastic, clear vs. amber or opaque, cap liners) and for anticipating interactions when mixing drugs

and dosage forms. Stability and expiration dating are based on reaction kinetics, i.e., the study of the rate of chemical change and the way this rate is influenced by conditions of concentration of reactants, products, and other chemical species that may be present, and by factors such as solvent, pressure, and temperature.

In considering chemical stability of a pharmaceutical, one must know the reaction order and reaction rate. The reaction order may be the overall order (the sum of the exponents of the concentration terms of the rate expression), or the order with respect to each reactant (the exponent of the individual concentration term in the rate expression).

Rate Reactions

The reaction rate expression is a description of the drug concentration with respect to time. Most commonly, zero-order and first-order reactions are encountered in pharmacy. These are presented in the physical pharmacy capsule "Rate Reactions," along with some appropriate examples.

Q_{10} Method of Shelf-Life Estimation

The Q_{10} method of shelf-life estimation allows the pharmacist quickly to calculate estimates of shelf-life for a product that may have been stored or is going to be stored under a different set of conditions. It is explained in the physical pharmacy capsule "Q_{10} Method of Shelf-Life Estimation."

Enhancing Stability of Drug Products

Many pharmaceutic ingredients may be utilized in preparing the desired dosage form of a drug substance. Some of these agents may be used to achieve the desired physical and chemical characteristics of the product or to enhance its appearance, odor, and taste. Other substances may be used to increase the stability of the drug substance, particularly against the hydrolytic and oxidative processes. In each instance, the added pharmaceutic ingredient must be compatible with and must not detract from the stability of the drug substance in the particular dosage form prepared.

There are several approaches to the stabilization of pharmaceutical preparations containing drugs subject to deterioration by hydrolysis. Perhaps the most obvious is the reduction, or better yet, the elimination of water from the pharmaceutical system. Even solid dosage forms containing water-labile drugs must be protected from the humidity of the atmosphere. This may be accomplished by applying a waterproof-protective coating over tablets or by enclosing and maintaining the drug in tightly closed containers. It is not unusual to detect

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Physical Pharmacy Capsule 3.8   **Rate Reactions**

ZERO ORDER RATE REACTIONS

If the loss of drug is independent of the concentration of the reactants and constant with respect to time (i.e., 1 mg/mL/hour), the rate is called zero order. The mathematical expression is:

$$\frac{-dC}{dt} = k_0$$

where k_0 is the zero-order rate constant [concentration(C)/time(t)].

The integrated, and more useful form of the equation, is:

$$C = -k_0 t + C_0$$

where C_0 is the initial concentration of the drug.

EXAMPLE 1

A drug suspension (125 mg/mL) decays by zero-order kinetics with a reaction rate constant of 0.5 mg/mL/hour. What is the concentration of intact drug remaining after 3 days (72 hours)?

$$C = -(0.5 \text{ mg/mL/hr}) \, (72 \text{ hr}) + 125 \text{ mg/mL}$$

$$C = 89 \text{ mg/mL}$$

EXAMPLE 2

How long will it take for the suspension to reach 90% of its original concentration?

$$90\% \times 125 \text{ mg/mL} = 112.5 \text{ mg/mL}$$

$$t = \frac{C - C_0}{-k_0} - \frac{112.5 \text{ mg/mL} - 125 \text{ mg/mL}}{-0.5 \text{ mg/mL/hr}} = 25 \text{ hours}$$

Drug suspensions are examples of pharmaceuticals that ordinarily follow zero-order kinetics for degradation.

FIRST ORDER RATE REACTIONS

If the loss of drug is directly proportional to the concentration remaining with respect to time, it is called a first-order reaction and has the units of reciprocal time, i.e., time^{-1}. The mathematical expression is:

$$\frac{-dC}{dt} = kC$$

where C is the concentration of intact drug remaining, t is time, $(-dC/dt)$ is the rate at which the intact drug degrades, and k is the specific reaction rate constant.

The integrated and more useful form of the equation is:

$$\log C = \frac{-kt}{2.303} + \log C_0$$

where C_0 is the initial concentration of the drug.

In natural log form, the equation is:

$$\ln C = -kt + \ln C_0$$

EXAMPLE 3

An ophthalmic solution of a mydriatic drug, present at a 5 mg/mL concentration, exhibits first-order degradation with a rate of 0.0005/day. How much drug will remain after 120 days?

$$\ln C = -(0.0005/\text{day}) \, (120) + \ln (5 \text{ mg/mL})$$

$$\ln C = -0.06 + 1.609$$

$$\ln C = 1.549$$

$$C = 4.71 \text{ mg/mL}$$

Rate Reactions (Continued)

EXAMPLE 4

In the above example, how long will it take for the drug to degrade to 90% of its original concentration?

$$90\% \text{ of } 5 \text{ mg/mL} = 4.5 \text{ mg/mL}$$

$$\ln 4.5 \text{ mg/mL} = -(0.0005/\text{day})t + \ln (5 \text{ mg/mL})$$

$$t = \frac{\ln 4.5 \text{ mg/mL} - \ln 5 \text{ mg/mL}}{-0.0005/\text{day}}$$

$$t = 210 \text{ days}$$

Stability projections for shelf-life (t_{90}) (i.e., the time required for 10% of the drug to degrade with 90% of the intact drug remaining, are commonly based on the Arrhenius equation:

$$\log \frac{k_2}{k_1} = \frac{Ea (t_2 - T_1)}{2.3 \, RT_1 T_2}$$

which relates the reaction rate constants (k) to temperatures (T) with the gas constant (R) and the energy of activation (Ea).

The relationship of the reaction rate constants at two different temperatures provides the energy of activation for the degradation. By performing the reactions at elevated temperatures, instead of allowing the process to proceed very slowly at room temperature, the Ea can be calculated and a k value for room temperature determined by using the Arrhenius equation.

EXAMPLE 5

The degradation of a new cancer drug follows first-order kinetics and has first-order degradation rate constants of 0.0001/hr at 60°C and 0.0009 at 80°C. What is its Ea?

$$\log \frac{(0.0009)}{(0.0001)} = \frac{EA (353 - 333)}{(2.3)(1.987)(353)(333)}$$

$$Ea = 25,651 \text{ kcal/mol}$$

hydrolyzed aspirin by noticing an odor of acetic acid upon opening a bottle of aspirin tablets. In liquid preparations, water can frequently be replaced or reduced in the formulation through the use of substitute liquids such as glycerin, propylene glycol, and alcohol. In certain injectable products, anhydrous vegetable oils may be used as the drug's solvent to reduce the chance of hydrolytic decomposition.

Decomposition by hydrolysis may be prevented for other drugs to be administered in liquid form by suspending them in a non-aqueous vehicle rather than by dissolving them in an aqueous solvent. In still other instances, particularly for certain unstable antibiotic drugs, when an aqueous preparation is desired, the drug may be supplied to the pharmacist in a dry form for *reconstitution* by adding a specified volume of purified water just before dispensing. The dry powder supplied commercially is actually a mixture of the antibiotic, suspending agents, flavorants, and colorants, which, when reconstituted by the pharmacist, remains a stable suspension or solution of the drug for the time period in which the preparation is normally consumed. Storage under refrigeration is advisable for most preparations considered unstable due to hydrolytic causes. Together with temperature, pH is a major determinant in the stability of a drug prone to hydrolytic decomposition. The hydrolysis of most drugs is dependent upon the relative concentrations of the hydroxyl and hydronium ions, and a pH at which each drug is optimally stable can be easily determined. For most hydrolyzable drugs the pH of optimum stability is on the acid side, somewhere between pH 5 and 6. Therefore, through judicious use of buffering agents, the stability of otherwise unstable compounds can be increased.

Physical Pharmacy Capsule 3.9 Q_{10} Method of Shelf-Life Estimation

The Q_{10} approach, based on Ea, is independent of reaction order and is described as:

$$Q_{10} = e^{\{(Ea/R)[(1/T+10) - (1/T)]\}}$$

where Ea is the energy of activation,
      R is the gas constant, and
      T is the absolute temperature.
      In usable terms, Q_{10} is the ratio of two different reaction rate constants, and is defined as:

$$Q_{10} = \frac{K_{(T+10)}}{K_T}$$

Q values of 2, 3 and 4 are commonly used and relate to the energies of activations of the reactions for temperatures around room temperature (25°C). For example, a Q value of 2 corresponds to an Ea (kcal/mol) of 12.2, a Q value of 3 corresponds to an Ea of 19.4, and a Q value of 4 corresponds to an Ea of 24.5.

Reasonable estimates can often be made using the value of 3.

The equation to use for Q_{10} shelf-life estimates is:

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}}$$

where $t_{90}T_2$ is the estimated shelf-life,
      $t_{90}T_1$ is the given shelf-life at a given temperature, and
      ΔT is the difference in the temperatures T_1 and T_2.
      As is evident from this relationship, an increase in ΔT will decrease the shelf-life and a decrease in ΔT will increase shelf-life. This is the same as saying that storing at a warmer temperature will shorten the life of the drug and storing at a cooler temperature will increase the life of the drug.

EXAMPLE 1
An antibiotic solution has a shelf-life of 48 hours in the refrigerator (5°C). What is its estimated shelf-life at room temperature (25°C)?

Using a Q value of 3, we set up the relationship as follows.

$$t_{90}(T_2) = \frac{t_{90}(T_1)}{Q_{10}^{(\Delta T/10)}} = \frac{48}{3^{[(25-5)/10]}} = \frac{48}{3^2} = 5.33 \text{ hours}$$

EXAMPLE 2
An ophthalmic solution has a shelf-life of 6 hours at room temperature (25°C). What would be the estimated shelf-life if stored in a refrigerator (5°C)? (*Note:* Since the temperature is decreasing, ΔT will be negative.)

$$t_{90}(T_2) = \frac{6}{3^{[(5-25)/10]}} = \frac{6}{3^{-2}} = 6 \times 3^2 = 54 \text{ hours}$$

Pharmacists should keep in mind that these are estimates, and actual energies of activation can be often be obtained from the literature for more exact calculations.

Buffers are used to maintain a certain pH as described in the physical pharmacy capsule entitled "Buffer Capacity."

Pharmaceutically, the oxidation of a susceptible drug substance is most likely to occur when it is maintained in other than the dry state in the presence of oxygen, exposed to light, or combined in formulation with other chemical agents without proper regard to their influence on the oxidation process. The oxidation of a chemical in a pharmaceutical preparation is usually attendant with an alteration in the color of that preparation. It may also result in precipitation or a change in the usual odor of a preparation.

Physical Pharmacy Capsule 3.10   **Buffer Capacity**

pH, buffers and buffer capacity are especially important in drug product formulation; especially as they are involved in drug solubility, drug activity, drug absorption drug stability and patient comfort.

A buffer is a system, usually an aqueous solution, that can resist changes in pH upon addition of an acid or base. Buffers are composed of a weak acid and its conjugate base, or a weak base and its conjugate acid. Buffers are prepared by:

  a. mixing a weak acid and its conjugate base or a weak base and it's conjugate acid, or
  b. mixing a weak acid and a strong base to form the conjugate base or a weak base and a strong acid to form the conjugate acid

Using the Henderson-Hasselbach equation:

$$pH = pKa + \log (base/acid)$$

(Remember that the acid is the proton donor and the base is the proton acceptor)

EXAMPLE 1
A buffer is prepared by mixing 100 mL of 0.2 M phosphoric acid with 200 mL of 0.08 M sodium phosphate monobasic. What is the pH of this buffer? (K_a of phosphoric acid = 7.5×10^{-3})

Moles acid = (0.2 mol/1000 mL)(100 mL) = 0.02 mol; (0.02 mol)/(0.3 L) = 0.067 M

Moles base = (0.08 mol/1000 mL)(200 mL) = 0.016 mol; (0.016 mol)/(0.3 L) = 0.053 M

pKa = $-\log 7.5 \times 10^{-3}$ = 2.125

pH = 2.125 + log (0.016 mol/0.02 mol) = 2.028

EXAMPLE 2
Determine the pH of the buffer prepared as shown below.

Sodium acetate 50 g

Conc. HCl 10 mL

Water q.s. 2 L

Helpful numbers:

pK$_a$ acetic acid = 4.76

m.w. sodium acetate = 82.08

m.w. acetic acid = 60.05

m.w. HCl = 36.45

Conc.HCl ≈ 44% HCl w/v

NaAc   +   HCl   →   NaCl   +   HAc   +   NaAc

(0.609 mol)   (0.121 mol)   (0.121 mol)   ((0.121 mol)   (0.488 mol)
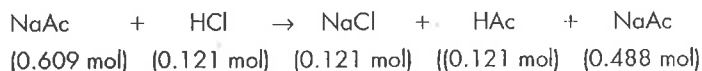
HCl: {(10 mL) [(44g)/(100 mL)] (l mol)/(36.45g)} = 0.121 mol

NaAc: {(50 g)[(1 mol)/(82.08g)] = 0.609 mol
        (0.609 mol) − (0.121 mol) = 0.488 mol

pH = 4.76 + log (0.488 mol)/(0.121 mol) = 5.367

The ability of a buffer solution to resist changes in pH upon the addition of an acid or a base is called buffer capacity (β) and is defined as:

$$\beta = \Delta B/\Delta pH$$

where ΔB = molar concentration of acid or base added
    ΔpH = change in pH due to addition of acid or base
    ΔpH can be determined experimentally or calculated using the Henderson-Hasselbach equation.

Buffer Capacity (Continued)

EXAMPLE 3

If 0.2 mole of HCl is added to a 0.015 M solution of ammonium hydroxide and the pH falls from 9.5 to 8:9, what is the buffer capacity?

$$\Delta pH = 9.5 - 8.9 = 0.6$$
$$\Delta B = 0.2 \text{ mol/L} = 0.2 \text{ M}$$
$$\beta = 0.2 \text{ M}/0.6 = 0.33 \text{ M}$$

EXAMPLE 4

If 0.002 mole of HCl is added to the buffer in Example No. 1, what is its buffer capacity? After adding 0.002 mole HCl:

$$H_3PO_4: 0.02 \text{ mol} + 0.002 \text{ mol} = 0.022 \text{ mol}$$
$$NaH_2PO_4: 0.016 \text{ mol} - 0.002 \text{ mL} = 0.014 \text{ mol}$$
$$pH = 2.125 + \log (0.014 \text{ mol}/0.022 \text{ mol}) = 1.929$$
$$\Delta pH = 2.028 - 1.929 = 0.099$$
$$\Delta AB = 0.002 \text{ mol}/0.3 \text{ L} = 0.0067 \text{ M}$$
$$\beta = 0.0067 \text{ M}/0.099 = 0.067 \text{ M}$$

Another approach to calculating buffer capacity involves the use of Van-Slyke's equation, given as:

$$\beta = 2.3C \{Ka[H^+]/(Ka[H^+])^2\}$$

where C = sum of the molar concentrations of the acid and base, and

$$[H^+] = 10^{-pH}$$

EXAMPLE 5

What is the Van Slyke's buffer capacity of the buffer prepared in Example No. 1?

$$C = 0.0067 \text{ M} + 0.0053 \text{ M} = 0.12 \text{ M}$$
$$Ka = 7.5 \times 10^{-3}$$
$$[H+] = 10^{-2.028} = 9.38 \times 10^{-3} \text{ M}$$
$$\beta = 2.3(0.12M)\{[(7.5\times10^{-3}M)(9.38 \times 10^{-3}M)/[(7.5 \times 10^{-3}M)/(9.38 \times 10^{-3}M)^2]\} = 0.68 \text{ M}$$

The oxidative process is diverted, and the stability of the drug is preserved by agents called *antioxidants*, which react with one or more compounds in the drug to prevent progress of the chain reaction. In general, antioxidants act by providing electrons and easily available hydrogen atoms that are accepted more readily by the free radicals than are those of the drug being protected. Various antioxidants are employed in pharmacy. Among those more frequently used in aqueous preparations are sodium sulfite (Na_2SO_3), sodium bisulfite ($NaHSO_3$), hypophosphorous acid (H_3PO_2), and ascorbic acid. In oleaginous (oily or unctuous) preparations, alpha-tocopherol, butylhydroxyanisole, and ascorbyl palmitate find application.

In June 1987, FDA labeling regulations went into

effect requiring a warning about possible allergic-type reactions, including anaphylaxis in the package insert for prescription drugs to which sulfites have been added to the final dosage form. Sulfites are used as preservatives in many injectable drugs, such as antibiotics and local anesthetics. Some inhalants and ophthalmic preparations also contain sulfites, but relatively few oral drugs contain these chemicals. The purpose of the regulation is to protect the estimated 0.2% of the population who suffer allergic reactions from the chemicals. Many of the sulfite-sensitive persons suffer from asthma or other allergic conditions. Previous to the regulations dealing with prescription medication, the FDA issued regulations for the use of sulfites in food. Asthmatics and other patients who may be sulfite-

sensitive should be reminded to read the labels of packaged foods and medications to check for the presence of these agents. Sulfiting agents covered by the regulations are potassium bisulfite, potassium metabisulfite, sodium bisulfite, sodium metabisulfite, sodium sulfite and sulfur dioxide. The FDA permits the use of sulfites in prescription products, with the proper labeling, because there are no generally suitable substitutes for sulfites to maintain potency in certain medications. Some, but not all, epinephrine injections contain sulfites.

The proper use of antioxidants involves their specific application only after appropriate biomedical and pharmaceutical studies. In certain instances other pharmaceutical additives can inactivate a given antioxidant when used in the same formulation. In other cases certain antioxidants can react chemically with the drugs they were intended to stabilize, without a noticeable change in the appearance of the preparation.

Because the stability of oxidizable drugs may be adversely affected by oxygen, certain pharmaceuticals may require an oxygen-free atmosphere during their preparation and storage. Oxygen may be present in pharmaceutical liquids in the airspace within the container or may be dissolved in the liquid vehicle. To avoid these exposures, oxygen-sensitive drugs may be prepared in the dry state and they, as well as liquid preparations, may be packaged in sealed containers with the air replaced by an inert gas such as nitrogen. This is common practice in the commercial production of vials and ampuls of easily oxidizable preparations intended for parenteral use.

Trace metals originating in the drug, solvent, container, or stopper are a constant source of difficulty in preparing stable solutions of oxidizable drugs. The rate of formation of color in epinephrine solutions, for instance, is greatly increased by the presence of ferric, ferrous, cupric, and chromic ions. Great care must be taken to eliminate these trace metals from labile preparations by thorough purification of the source of the contaminant or by chemically complexing or binding the metal through the use of specialized agents that make it chemically unavailable for participation in the oxidative process. These agents are referred to as chelating agents and are exemplified by calcium disodium edetate and ethylenediamine tetra-acetic acid (EDTA).

Light can also act as a catalyst to oxidation reactions. As a photocatalyst, light waves transfer their energy (photon) to drug molecules, making the latter more reactive through increased energy capability. As a precaution against the acceleration of the oxidative process, sensitive preparations are packaged in light-resistant or opaque containers.

Because most drug degradations proceed more rapidly with an advanced temperature, it is also advisable to maintain oxidizable drugs in a cool place. Another factor that could affect the stability of an oxidizable drug in solution is the pH of the preparation. Each drug must be maintained in solution at the pH most favorable to its stability. This, in fact, varies from

Table 3.2. Examples of Some Official Drugs and Preparations Especially Subject to Chemical or Physical Deterioration

Preparation	Category	Monograph or Label Warning
Epinephrine Bitartrate Ophthalmic Solution, USP Epinephrine Inhalation Solution, USP Epinephrine Injection, USP Epinephrine Nasal Solution, USP Epinephrine Ophthalmic Solution, USP	Adrenergic	Do not use the inhalation, injection, nasal or ophthalmic solution if it is brown or contains a precipitate.
Isoproterenol Sulfate Inhalation, Solution, USP Isoproterenol Inhalation Solution, USP	Adrenergic (bronchodilator)	Do not use the inhalation or injection if it is pink to brown in color or contains a precipitate.
Nitroglycerin Tablets, USP	Antianginal	To prevent loss of potency, keep these tablets in the original container or in a supplemental nitroglycerin container specifically labeled as being suitable for nitroglycerin tablets.
Paraldehyde, USP	Hypnotic	Paraldehyde is subject to oxidation to form acetic acid.

preparation to preparation and must be determined on an individual basis for the drug in question.

Statements in the USP, as those in Table 3.2, warn of the oxidative decomposition of drugs and preparations. In some instances the specific agent to employ as a stabilizer is mentioned in the monograph, and in others the term "suitable stabilizer" is used. An example in which a particular agent is designated for use is in the monograph for Potassium Iodide Oral Solution, USP. Potassium iodide in solution is prone to photocatalyzed oxidation and the release of free iodine with a resultant yellow to brown discoloration of the solution. The use of light-resistant containers is essential to its stability. As a further precaution against decomposition if the solution is not to be used within a short time, the USP recommends the addition of 0.5 mg of sodium thiosulfate for each gram of potassium iodide in the preparation. In the event free iodine is released during storage, the sodium thiosulfate converts it to colorless and soluble sodium iodide:

$$I_2 + 2Na_2S_2O_3 \longrightarrow 2\,NaI + Na_2S_4O_6$$
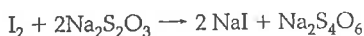
In summary, for easily oxidizable drugs, the formulation pharmacist may stabilize the respective preparations by the selective exclusion from the system of oxygen, oxidizing agents, trace metals, light, heat, and other chemical catalysts to the oxidation process. Antioxidants, chelating agents, and buffering agents may be added to create and maintain a favorable pH.

In addition to oxidation and hydrolysis, other destructive processes such as polymerization, chemical decarboxylation, and deamination may occur in pharmaceutical preparations. However, these processes occur less frequently and are peculiar to only small groups of chemical substances. Drug polymerization involves a reaction between two or more identical molecules with resultant formation of a new and generally larger molecule. Formaldehyde is an example of a drug capable of polymerization. In solution it may polymerize to paraformaldehyde $(CH_2O)_n$, a slowly soluble white crystalline substance that may cause the solution to become cloudy. The formation of paraformaldehyde is enhanced by cool storage temperatures, especially in solutions with high concentrations of formaldehyde. The official formaldehyde solution contains approximately 37% formaldehyde and according to the USP should be stored at temperatures not below 15°C (59°F). If the solution becomes cloudy upon standing in a cool place, it usually may be cleared by gentle warming.

Formaldehyde is prepared by the limited oxidation of methanol (methyl alcohol), and the USP permits a residual amount of this material to remain in the final product, since it has the ability to retard the formation of paraformaldehyde. Formaldehyde solution must be maintained in tight containers because oxidation of the formaldehyde yields formic acid.

$$\underset{\text{methanol}}{CH_3OH} \xrightarrow{(O)} \underset{\text{formaldehyde}}{HCHO} \xrightarrow{(O)} \underset{\text{formic acid}}{HCOOH}$$

Other organic drug molecules may be degraded through processes in which one or more of their active chemical groups are removed. These processes may involve various catalysts, including light and enzymes. Decarboxylation and deamination are examples of such processes, with the former involving the decomposition of an organic acid (R•COOH) and the consequent release of carbon dioxide gas and the latter involving the removal of the nitrogen-containing group from an organic amine. For example, insulin, a protein, deteriorates rapidly in acid solutions, due to extensive deamination. (3) Thus, most preparations of insulin are neutralized to reduce its rate of decomposition.

Stability Testing

The Food and Drug Administration's Current Good Manufacturing Practice regulations include sections on the stability and stability testing of pharmaceutical components and finished pharmaceutical products. In addition, agency and International Conference on Harmonization (ICH) guidelines and guidances provide working recommendations to support the regulatory requirements. Among these are the following (4):

"Stability Testing of New Drug Substances and Products"
"Quality of Biotechnological Products: Stability Testing of Biotechnology/Biological Drug Products"
"Photostability Testing of New Drug Substances and Products"
"Stability Testing of New Dosage Forms"

Drug and drug product stability testing during every stage of development is critical to the quality of the pharmaceutical product. Drug stability is important during preclinical testing and in clinical (human) trials in order to obtain a true and accurate assessment of the drug/drug product being

evaluated. For a marketed drug product, assurance of drug stability is vital to the safety and effectiveness of the product when distributed and during the entire course of its shelf-life and use.

The FDA-required demonstration of drug stability is necessarily different for each stage of drug development, i.e., for a 2-week preclinical study, an early Phase I study, a limited Phase II trial, a pivotal Phase III clinical study, or for a New Drug Application for approval for marketing. As a drug development program progresses, so does the requisite data to demonstrate and document the drug/drug product's stability profile. Before approval for marketing, a product's stability must be assessed with regard to its formulation, the influence of pharmaceutic ingredients present, the influence of the container and closure, the manufacturing and processing conditions (e.g. heat), packaging components and conditions of warehousing/storage, the anticipated conditions of shipping, temperature, light and humidity, and anticipated duration and conditions of pharmacy shelf-life and patient utilization. It is important to recognize, that the "holding" of intermediate product components (as drug granulations for tableting) for undue lengthy periods before processing into finished pharmaceutical products could affect the stability of both the intermediate component and the finished product. Therefore, in-process stability testing including the retesting of intermediate components is important.

Product containers, closures, and other packaging features must be considered in stability testing. For instance, tablets or capsules packaged in glass or plastic bottles, blister packs or strip packaging would require different stability test protocols. Drugs particularly subject to hydrolysis or oxidative decomposition must be evaluated accordingly. And, parenteral and other sterile products must meet sterility test standards to ensure protection against microbial contamination. Any preservatives used must be tested for effectiveness in the finished product.

As noted elsewhere in this section, drug products must meet stability standards for long-term storage at room temperatures and under conditions of relative humidity. Products are also subjected to accelerated stability studies as an indication of shelf-life stability. It is an FDA requirement that if not submitted in the approved application, the first three postapproval production batches of a drug substance be placed on long-term stability studies and the first three postapproval production batches of drug product be subject to both long-term and accelerated stability studies (5,6).

Drug instability in pharmaceutical formulations may be detected in some instances by a change in the physical appearance, color, odor, taste or texture of the formulation whereas in other instances chemical changes may occur which are not self-evident and may only be ascertained through chemical analysis. Scientific data pertaining to the stability of a formulation leads to the prediction of the expected shelf-life of the proposed product and, when necessary, to the redesign of the drug (e.g. into more stable salt or ester form) and to the reformulation of the dosage form. Obviously the rate or speed at which drug degradation occurs in a formulation is of prime importance. The study of the rate of chemical change and the way in which it is influenced by such factors as the concentration of the drug or reactant, the solvent employed, the conditions of temperature and pressure, and the presence of other chemical agents in the formulation is termed reaction kinetics.

In general a kinetic study begins by measuring the concentration of the drug being examined at given time intervals under a specific set of conditions including temperature, pH, ionic strength, light intensity, and drug concentration. The measurement of the drug's concentration at the various time intervals reveals the stability or instability of the drug under the specified conditions with the passage of time. From this starting point, each of the original conditions may be varied on an individual basis to determine the influence that such changes make on the drug's stability. For example, the pH of the solution may be changed, whereas the temperature, light intensity, and original drug concentration remain as they were in the original or baseline experiment.

The data collected may be presented graphically, by plotting the drug concentration as a function of time. From the experimental data, the reaction rate may be determined and a rate constant and half-life calculated.

The use of exaggerated conditions of temperature, humidity, light, and others, to test the stability of drug formulations is termed accelerated stability testing. Accelerated temperature stability studies, for example, may be conducted for six months at 40°C with 75% relative humidity. If a significant change occurs in the drug/drug product under these conditions, lesser temperature and humidity may be used, such as 30°C and 60% relative humidity. The use of short-term accelerated studies is for the purpose of determining the most stable of the proposed formulations for a drug product. In stress testing, temperature elevations, in 10°

increments higher than used in accelerated studies, are employed until chemical or physical degradation. Once the most stable formulation is ascertained, its long-term stability is predicted from the data generated from continuing stability studies. Depending on the types and severity of conditions employed, it is not unusual to maintain samples under exaggerated conditions of both temperature and varying humidity for periods of 6 to 12 months. Such studies lead to the prediction of shelf-life for a drug product.

In addition to the accelerated stability studies, drug products are also subjected to long-term stability studies under the usual conditions of transport and storage expected during product distribution. In conducting these studies, the different climatic zones, nationally and internationally, to which the product may be subjected must be borne in mind, and expected variances in conditions of temperature and humidity included in the study design. Geographic regions of the world are defined by climatic zones: zone I, "temperate"; zone II, "subtropical"; zone III, "hot and dry"; and zone IV, "hot and humid." A given drug product may encounter more than a single zone of temperature/humidity variations during its production and shelf-life. Further, it may be warehoused, transported, placed on a pharmacy's shelf, and subsequently in the patient's medicine cabinet, over a varying time course and at a wide range of temperature and humidity. In general, however, the long-term (12 months minimum) testing of new drug entities is conducted at 25° C ± 2° C and at a relative humidity of 60% ± 5%. Samples maintained under these conditions may be retained for periods of 5 years or longer during which time they are observed for physical signs of deterioration and chemically assayed. These studies, considered with the accelerated stability studies previously performed, then lead to a more precise determination of drug product stability, actual shelf-life, and the possible extension of expiration dating.

When chemical degradation products are detected, the FDA requires the manufacturer to report their chemical identities, including structures, mechanism of formation, physical and chemical properties, procedures for isolation and purification, specifications and directions for determination at levels expected to be present in the pharmaceutical product, and the pharmacologic action and biologic significance, if any, to their presence.

In addition, signs of degradation of the specific dosage forms must be observed and reported. For the various dosage forms, this includes the following (1).

Tablets: appearance, friability, hardness, color, odor, moisture content, and dissolution.

Capsules: strength, moisture, color, appearance, shape, brittleness, and dissolution.

Oral solutions and suspensions: appearance, strength, pH, color, odor, redispersibility (suspensions), and clarity (solutions).

Oral powders: appearance, strength, color, odor, moisture.

Metered-dose inhalation aerosols: strength, delivered dose per actuation, number of metered doses, color, particle-size distribution, loss of propellant, pressure, valve corrosion, spray pattern, absence of pathogenic microorganisms.

Topical nonmetered aerosols: appearance, odor, pressure, weight loss, net weight dispensed, delivery rate, and spray pattern.

Topical creams, ointments, lotions, solutions, and gels: appearance, color, homogeneity, odor, pH, resuspendibility (lotions), consistency, particle-size distribution, strength, weight loss.

Ophthalmic preparations: appearance, color, consistency, pH, clarity (solutions), particle size and resuspendibility (suspensions, creams, ointments), strength, and sterility.

Small-volume parenterals: strength, appearance, color, particulate matter, dispersibility (suspensions), pH, sterility, pyrogenicity, and closure integrity.

Large-volume parenterals: strength, appearance, color, clarity, particulate matter, pH, volume and extractables (when plastic containers are used), sterility, pyrogenicity, and closure integrity.

Suppositories: strength, softening range, appearance, and dissolution.

Emulsions: appearance (as phase separation), color, odor, pH, viscosity, and strength.

Controlled-release membrane drug delivery systems: seal strength of the drug reservoir, decomposition products, membrane integrity, drug strength, and drug release rate.

Under usual circumstances, most manufactured products require a shelf-life of 2 or more years to ensure their stability at the time of patient consumption. Commercial products must bear an appropriate expiration date. This date identifies the time during which the product may be expected to maintain its potency and remain stable under the designated storage conditions. The expiration date

limits the time during which the product may be dispensed by the pharmacist or used by the patient.

Prescriptions requiring extemporaneous compounding by the pharmacist do not require the extended shelf-life that commercially manufactured and distributed products do because they are intended to be used immediately on their receipt by the patient and used only during the immediate course of the prescribed treatment. However, these compounded prescriptions must remain stable and efficacious during the course of their use and the compounding pharmacist must employ formulative components and techniques which will result in a stable product (7).

In years past pharmacists were confronted primarily with innocuous, topical prescriptions that required extemporaneous formulation. However, in recent years there has been a need to compound other drug delivery systems as well, e.g., progesterone vaginal suppositories, oral suspensions, from existing tablets or capsules. When presented with a prescription that requires extemporaneous compounding, the pharmacist is confronted with a difficult situation because the potency and the stability of these prescriptions is a serious matter. Occasionally, the results of compatibility and stability studies on such prescriptions are published in scientific and professional journals. These are very useful; however, there are also prescriptions for which stability and compatibility information is not readily available. In these instances, it behooves the pharmacist to at least contact the drug manufacturer of the active ingredient(s) to solicit stability information. Also, a compilation of published stability information is included in Trissel's Stability of Compounded Formulations (8). The published stability data are applicable only to products that are prepared identically to the products that are reported.

USP guidelines on stability of extemporaneous compounded formulations state that, in the absence of stability information that is applicable to a specific drug and preparation, the following guidelines can be utilized: nonaqueous liquids and solid formulations where the manufactured drug is the source of the active ingredient–not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier; nonaqueous liquids and solid formulations where a USP or NF substance is the source of active ingredient—a beyond-use date of 6 months; for water-containing formulations prepared from ingredients in solid form—a beyond-use date of not later than 14 days when stored at cold temperatures; for all other formulations—a beyond-use date of the intended du-

ration of therapy or 30 days, whichever is earlier (9). Thus, in the instance where an oral aqueous liquid preparation is made from an existing tablet or capsule formulation, the pharmacist should make up only at most a 14 days supply and it must be stored in a refrigerator. Further, the pharmacist must also dispense the medication in a container conducive to stability and use and must advise the patient of the proper method of use and conditions of storage of the medication.

Finally, when compounding on the basis of extrapolated or less than concrete information it is best for the pharmacist to keep the formulation simple and not to shortcut but use the necessary pharmaceutical adjuvants to prepare the prescription.

Pharmaceutic Ingredients

Definitions and Types

To prepare a drug substance into a final dosage form, pharmaceutic ingredients are required. For example, in the preparation of pharmaceutic solutions, one or more *solvents* are used to dissolve the drug substance, *flavors and sweeteners* are used to make the product more palatable, *colorants* are added to enhance product appeal, *preservatives* may be added to prevent microbial growth and *stabilizers*, such as antioxidants and chelating agents, may be used to prevent drug decomposition, as previously discussed. In the preparation of tablets, *diluents* or *fillers* are commonly added to increase the bulk of the formulation, *binders* to cause the adhesion of the powdered drug and pharmaceutic substances, *antiadherents* or *lubricants* to assist the smooth tableting process, *disintegrating agents* to promote tablet break-up after administration, and coatings to improve stability, control disintegration, or to enhance appearance. Ointments, creams, and suppositories achieve their characteristic features due to the pharmaceutic bases which are utilized. Thus, for each dosage form, the pharmaceutic ingredients establish the primary features of the product, and contribute to the physical form, texture, stability, taste and overall appearance.

Table 3.3 presents the principal categories of pharmaceutic ingredients, with examples of some of the official and commercial agents currently used. Additional discussion of many of the pharmaceutic ingredients may be found in the chapters where they are most relevant; for example, pharmaceutic materials used in tablet and capsule formulations

Table 3.3.   Examples of Pharmaceutic Ingredients

Ingredient Type	Definition	Examples
Acidifying Agent	Used in liquid preparations to provide acidic medium for product stability.	Citric acid Acetic acid Fumaric acid Hydrochloric acid Nitric acid
Alkalinizing Agent	Used in liquid preparations to provide alkaline medium for product stability.	Ammonia solution Ammonium carbonate Diethanolamine Monoethanolamine Potassium hydroxide Sodium borate Sodium carbonate Sodium hydroxide Triethanolamine Trolamine
Adsorbent	An agent capable of holding other molecules onto its surface by physical or chemical (chemisorption) means.	Powdered cellulose Activated charcoal
Aerosol Propellant	Agent responsible for developing the pressure within an aerosol container and expelling the product when the valve is opened.	Carbon dioxide Dichlorodifluoromethane Dichlorotetrafluoroethane Trichloromonofluoromethane
Air Displacement	Agent employed to displace air in a hermetically sealed container to enhance product stability.	Nitrogen Carbon dioxide
Antifungal Preservative	Used in liquid and semi-solid preparations to prevent the growth of fungi. The effectiveness of the parabens is usually enhanced when they are used in combination.	Butylparaben Ethylparaben Methylparaben Benzoic acid Propylparaben Sodium benzoate Sodium propionate
Antimicrobial Preservative	Used in liquid and semi-solid preparations to prevent the growth of microorganisms.	Benzalkonium chloride Benzethonium chloride Benzyl alcohol Cetylpyridinium chloride Chlorobutanol Phenol Phenylethyl alcohol Phenylmercuric nitrate Thimerosal
Antioxidant	Agent that inhibits oxidation and thus is used to prevent the deterioration of preparations by the oxidative process.	Ascorbic acid Ascorbyl palmitate Butylated hydroxyanisole Butylated hydroxytoluene Hypophophorous acid Monothioglycerol Propyl gallate Sodium ascorbate Sodium bisulfite Sodium formaldehyde Sulfoxylate Sodium metabisulfite
Buffering Agent	Used to resist change in pH upon dilution or addition of acid or alkali. potassium metaphosphate	Potassium phosphate, monobasic Sodium acetate Sodium citrate anhydrous and dihydrate

Table 3.3.   Examples of Pharmaceutic Ingredients

Ingredient Type	Definition	Examples
Chelating Agent	Substance that forms stable, water soluble complexes (chelates) with metals. Chelating agents are used in some liquid pharmaceuticals as stabilizers to complex heavy metals which might promote instability. In such use they are also called *sequestering* agents.	Edetic acid Edetate disodium
Colorant	Used to impart color to liquid and solid (e.g., tablets and capsules) pharmaceutical preparations.	FD&C Red No. 3 FD&C Red No. 20 FD&C Yellow No. 6 FD&C Blue No. 2 D&C Green No. 5 D&C Orange No. 5 D&C Red No. 8 Caramel Ferric oxide, red
Clarifying Agent	Used as a filtering aid because of adsorbent qualities.	Bentonite
Emulsifying Agent	Used to promote and maintain the dispersion of finely subdivided particles of a liquid in a vehicle in which it is immiscible. The end product may be a liquid emulsion or semisolid emulsion (e.g., a cream).	Acacia Cetomacrogol Cetyl alcohol Glyceryl monostearate Sorbitan monooleate Polyoxyethylene 50 stearate
Encapsulating Agent	Used to form thin shells for the purpose of enclosing a drug substance or drug formulation for ease of administration.	Gelatin Cellulose acetate phthalate
Flavorant	Used to impart a pleasant flavor and often odor to a pharmaceutical preparation. In addition to the natural flavorants listed, many synthetic flavorants are also used.	Anise oil Cinnamon oil Cocoa Menthol Orange oil Peppermint oil Vanillin
Humectant	Used to prevent the drying out of preparations—particularly ointments and creams—due to the agent's ability to retain moisture.	Glycerin Propylene glycol Sorbitol
Levigating Agent	Liquid used as an intervening agent to reduce the particle size of a drug powder by grinding together, usually in a mortar.	Mineral oil Glycerin
Ointment Base	Semisolid vehicle into which drug substances may be incorporated in preparing medicated ointments.	Lanolin Hydrophilic ointment Polyethylene glycol ointment Petrolatum Hydrophilic petrolatum White ointment Yellow ointment Rose water ointment
Plasticizer	Used as a component of film-coating solutions to enhance the spread of the coat over tablets, beads, and granules.	Diethyl phthalate Glycerin
Solvent	An agent used to dissolve another pharmaceutic substance or a drug in the preparation of a solution. The solvent may be aqueous or nonaqueous (e.g., oleaginous). Cosolvents, such as water and alcohol (hydroalcoholic) and water and glycerin, may be used when needed. Solvents rendered sterile are used in certain preparations (e.g., injections).	Alcohol Corn oil Cottonseed oil Glycerin Isopropyl alcohol Mineral oil Oleic acid Peanut oil Purified water Water for injection Sterile water for injection Sterile water for irrigation

Table 3.3.   Examples of Pharmaceutic Ingredients

Ingredient Type	Definition	Examples
Stiffening Agent	Used to increase the thickness or hardness of a pharmaceutical preparation, usually an ointment.	Cetyl alcohol Cetyl esters wax Microcrystalline wax Paraffin Stearyl alcohol White wax Yellow wax
Suppository Base	Used as a vehicle into which drug substances are incorporated in the preparation of suppositories.	Cocoa butter Polyethylene glycols (mixtures)
Surfactant (surface active agent)	Substances that absorb to surfaces or interfaces to reduce surface or interfacial tension. May be used as wetting agents, detergents or emulsifying agents.	Benzalkonium chloride Nonoxynol 10 Oxtoxynol 9 Polysorbate 80 Sodium lauryl sulfate Sorbitan monopalmitate
Suspending Agent	A viscosity increasing agent used to reduce the rate of sedimentation of (drug) particles dispersed throughout a vehicle in which they are not soluble. The resultant suspensions may be formulated for use orally, parenterally, ophthalmically, topically, or by other routes.	Agar Bentonite Carbomer (e.g., Carbopol) Carboxymethylcellulose sodium Hydroxyethyl cellulose Hydroxypropyl cellulose Hydroxypropyl methylcellulose Kaolin Methylcellulose Tragacanth Veegum
Sweetening Agent	Used to impart sweetness to a preparation.	Aspartame Dextrose Glycerin Mannitol Saccharin sodium Sorbitol Sucrose
Tablet Antiadherents	Agents that prevent the sticking of tablet formulation ingredients to punches and dies in a tableting machine during production.	Magnesium stearate Talc
Tablet Binders	Substances used to cause adhesion of powder particles in tablet granulations.	Acacia Alginic acid Carboxymethylcellulose sodium Compressible sugar (e.g., Nu-Tab) Ethylcellulose Gelatin Liquid glucose Methylcellulose Povidone Pregelatinized starch
Tablet and Capsule Diluent	Inert substances used as fillers to create the desired bulk, flow properties, and compression characteristics in the preparation of tablets and capsules.	Dibasic calcium phosphate Kaolin Lactose Mannitol Microcrystalline cellulose Powdered cellulose Precipitated calcium carbonate Sorbitol Starch

continued

Table 3.3.   **Examples of Pharmaceutic Ingredients**

Ingredient Type	Definition	Examples
Tablet Coating Agent	Used to coat a formed tablet for the purpose of protecting against drug decomposition by atmospheric oxygen or humidity, to provide a desired release pattern for the drug substance after administration, to mask the taste or odor of the drug substance, or for aesthetic purposes. The coating may be of various types, including sugar-coating, film coating, or enteric coating. Sugar coating is water-based and results in a thickened covering around a formed tablet. Sugar-coated tablets generally start to break up in the stomach. A film coat is a thin cover around a formed tablet or bead. Unless it is an enteric coat, the film coat will dissolve in the stomach. An enteric-coated tablet or bead will pass through the stomach and break up in the intestines. Some coatings that are water-insoluble (e.g., ethylcellulose) may be used to coat tablets and beads to slow the release of drug as they pass through the gastrointestinal tract.	
Sugar coating:		Liquid glucose Sucrose
Film coating:		Hydroxyethyl cellulose Hydroxypropyl cellulose Hydroxypropyl methylcellulose Methylcellulose (e.g., Methocel) Ethylcellulose (e.g., Ethocel)
Enteric coating:		Cellulose acetate phthalate Shellac (35% in alcohol, ('pharmaceutical glaze")
Tablet Direct Compression Excipient	Used in direct compression tablet formulations.	Dibasic calcium phosphate (e.g., Ditab)

Tablet Disintegrant	Used in solid dosage forms to promote the disruption of the solid mass into smaller particles which are more readily dispersed or dissolved.	Alginic acid
		Carboxymethylcellulose
		   calcium
		Microcrystalline cellulose
		   (e.g., Avicel)
		Polacrilin potassium
		   (e.g., Amberlite)
		Sodium alginate
		Sodium starch glycollate
		Starch

Tablet Glidant	Agents used in tablet and capsule formulations to improve the flow properties of the powder mixture.	Colloidal silica Cornstarch Talc
Tablet Lubricant	Substances used in tablet formulations to reduce friction during tablet compression.	Calcium stearate Magnesium stearate Mineral oil Stearic acid Zinc stearate
Tablet/Capsule Opaquant	Used to render a capsule or a tablet coating opaque. May be used alone or in combination with a colorant.	Titanium dioxide
Tablet Polishing Agent	Used to impart an attractive sheen to coated tablets.	Carnauba wax White wax
Tonicity Agent	Used to render a solution similar in osmotic dextrose characteristics to physiologic fluids. Ophthalmic, parenteral, and irrigation fluids are examples of preparations in which tonicity is a consideration.	Sodium chloride

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Table 3.3. Examples of Pharmaceutic Ingredients

Ingredient Type	Definition	Examples
Vehicle	A carrying agent for a drug substance. They are used in formulating a variety of liquid dosage for oral and parenteral administration. Generally, oral liquids are aqueous preparations (as syrups) or hydroalcoholic (as elixirs). Parenteral solutions for intravenous use are aqueous, whereas intramuscular injections may be aqueous or oleaginous.	
Flavored/Sweetened		Acacia Syrup Aromatic Syrup Aromatic Elixir Cherry Syrup Cocoa Syrup Orange Syrup Syrup
Oleaginous		Corn Oil Mineral Oil Peanut Oil Sesame Oil
Sterile		Bacteriostatic Sodium chloride injection Bacteriostatic Water for Injection
Viscosity Increasing Agent	Used to change the consistency of a preparation to render it more resistant to flow. Used in suspensions to deter sedimentation, in ophthalmic solutions to enhance contact time (e.g., methylcellulose), to thicken topical creams, etc.	Alginic acid Bentonite Carbomer Carboxymethylcellulose Sodium Methylcellulose Povidone Sodium alginate Tragacanth

are discussed in Chapter 7, Capsules and Tablets and Chapter 8, Modified-Release Dosage Forms and Drug Delivery Systems.

Handbook of Pharmaceutical Excipients

The reader should also be aware of the *Handbook of Pharmaceutical Excipients* (10), which presents monographs on over 200 excipients used in pharmaceutical dosage form preparation. Included in each monograph is such information as: nonproprietary, chemical, and commercial names; empirical and chemical formulas and molecular weight; pharmaceutic specifications and chemical and physical properties; incompatibilities and interactions with other excipients and drug substances; regulatory status; and applications in pharmaceutic formulation or technology.

Harmonization of Standards

There is great interest currently in the international "harmonization" of standards applicable to pharmaceutical excipients. This is due to the fact that the pharmaceutical industry is multinational, with major companies having facilities in more than a single country, with products sold in markets worldwide, and with regulatory approval for these products required in each individual country. Standards for each drug substance and excipient used in pharmaceuticals are contained in pharmacopeias—or, for new agents, in an application for regulatory approval by the FDA or another nation's governing authority. The four pharmacopeias with the largest international use are the *United States Pharmacopeia/National Formulary* (USP/NF), *British Pharmacopeia* (BP), *European Pharmacopeia* (EP), and the *Japanese Pharmacopeia* (JP). Uniform standards for excipients in these and other pharmacopeias

would facilitate production efficiency, enable the marketing of a single formulation of a product internationally, and enhance regulatory approval of pharmaceutical products worldwide. The goal of harmonization is an ongoing effort undertaken by corporate representatives and international regulatory authorities.

A few of the more common and widely used pharmaceutical excipients, including sweeteners, flavors, colors and preservatives will be discussed here.

Appearance and Palatability

Although most drug substances in use today are unpalatable and unattractive in their natural state, modern pharmaceutical preparations present them to the patient as colorful, flavorful formulations attractive to the sight, smell, and taste. These qualities, which are the rule rather than the exception, have virtually eliminated the natural reluctance of many patients to take medications because of disagreeable odor or taste. In fact, the inherent attractiveness of today's pharmaceuticals has caused them to acquire the dubious distinction of being a source of accidental poisonings in the home, particularly among children who are lured by their organoleptic appeal.

There is some psychologic basis to drug therapy, and the odor, taste, and color of a pharmaceutical preparation can play a part. An appropriate drug will have its most beneficial effect when it is accepted and taken properly by the patient. The proper combination of flavor, fragrance, and color in a pharmaceutical product contributes to its acceptance.

Flavoring and Sweetening Pharmaceuticals

The flavoring of pharmaceuticals applies primarily to liquid dosage forms intended for oral administration. The 10,000 taste buds, found on the tongue, roof of the mouth, cheeks, and throat, have 60–100 receptor cells each (11). These receptor cells interact with molecules dissolved in the saliva and produce a positive or negative taste sensation. Medication in liquid form obviously comes into immediate and direct contact with these taste buds. By the addition of flavoring agents to liquid medication, the disagreeable taste of drugs may be successfully masked. Drugs placed in capsules or prepared as coated tablets may be easily swallowed with avoidance of contact between the drug and the taste buds. Tablets containing drugs that are not especially distasteful may remain uncoated and unflavored. Swallowing them with water usually is sufficient to avoid undesirable drug taste sensations. However, tablets of the chewable type as certain antacid and vitamin products, which are intended for mastication in the mouth, usually *are* sweetened and flavored to receive better patient acceptance.

The flavor sensation of a food or pharmaceutical is actually a complex blend of taste and smell with lesser influences of texture, temperature, and even sight. In flavor formulating a pharmaceutical product, the pharmacist must give consideration to the color, odor, texture, and taste of the preparation. It would be incongruous, for example, to color a liquid pharmaceutical red, give it a banana taste, and a mint odor. The color of a pharmaceutical must have a psychogenic balance with the taste, and the odor must also enhance that taste. Odor greatly affects the flavor of a preparation or foodstuff. If one's sense of smell is impaired, as during a head cold, the usual flavor sensation of food is similarly diminished.

The medicinal chemist and the formulation pharmacist are well acquainted with the taste characteristic of certain chemical types of drugs and strive to mask effectively the unwanted taste through the appropriate use of flavoring agents. Although there are no dependable rules for unerringly predicting the taste sensation of a drug based on its chemical constitution, experience permits the presentation of several observations. For instance, although we recognize and assume the salty taste of sodium chloride, the formulation pharmacist knows that all salts are not salty, but that their taste is a function of both the cation and anion. Whereas salty tastes are evoked by sodium, potassium, and ammonium chlorides and by sodium bromide, potassium and ammonium bromides elicit simultaneous bitter and salty sensations, and potassium iodide and magnesium sulfate (epsom salt) are predominantly bitter. In general, low molecular weight salts are salty, and higher molecular weight salts are bitter. With organic compounds, an increase in the number of hydroxyl groups (—OH) seems to increase the sweetness of the compound. Sucrose, which has eight hydroxyl groups, is sweeter than glycerin, another pharmaceutical sweetener, which has but three hydroxyl groups. In general, the organic esters, alcohols, and aldehydes are pleasant to the taste, and since many of them are volatile, they also contribute to the odor and thus the flavor of preparations in which they are used. Many nitrogen-containing compounds are extremely bitter, especially the plant alkaloids (as quinine), but certain other nitrogen-containing compounds are extremely sweet (as aspartame). The medicinal chemist recognizes that even the most simple structural change in an organic compound can alter its taste. D-glucose is sweet, but L-glucose has a

slightly salty taste; saccharin is very sweet, but N-methyl-saccharin is tasteless (12).

Thus, the predictability of the taste characteristics of a new drug is only speculative. However, it is soon learned, and the formulation pharmacist is then put to the task of increasing the drug's palatability in the environment of other formulative agents. The selection of an appropriate flavoring agent depends upon several factors, but primarily upon the taste of the drug substance itself. Certain flavoring materials are more effective than others in masking or disguising the particular bitter, salty, sour, or otherwise undesirable taste of medicinal agents. Although individuals' tastes and flavor preferences differ, cocoa-flavored vehicles are considered effective for masking the taste of bitter drugs. Fruit or citrus flavors are frequently used to combat sour or acid tasting drugs, and cinnamon, orange, raspberry, and other flavors have been successfully used to make preparations of salty drugs more palatable.

The age of the intended patient should also be considered in the selection of the flavoring agent, because certain age groups seem to prefer certain flavors. Children prefer sweet, candy-like preparations with fruity flavors, but adults seem to prefer less sweet preparations with a tart rather than a fruit flavor.

In addition to sucrose, a number of artificial sweetening agents have been utilized in foods and pharmaceuticals over the years. Some of these, as aspartame, saccharin and cyclamate, have faced challenges over their safety by the FDA and restrictions to their use and sale; in fact, the cyclamates were banned from use in the United States by the FDA in 1969.

The introduction of diet soft drinks in the 1950s provided the spark for the widespread use of artificial sweeteners today. Besides dieters, diabetics are regular users of artificial sweeteners. Over the years, each of the artificial sweeteners has undergone long periods of review and debate. Critical to the evaluation of food additives are issues of metabolism and toxicity. For example, almost none of the saccharin a person consumes is metabolized; it is excreted by the kidneys virtually unchanged. Cyclamate, on the other hand, is metabolized, or processed, in the digestive tract, and its byproducts are excreted by the kidneys. Aspartame breaks down in the body into three basic components: the amino acids phenylalanine and aspartic acid, and methanol. These three components, which also occur naturally in various foods, are in turn metabolized through regular pathways in the body. Be-

cause of its metabolism to phenylalanine, the use of aspartame by phenylketonurics is discouraged and diet foods and drinks must bear an appropriate label warning indicating that the particular foodstuff not be consumed by such individuals. Persons with phenylketonuria (PKU) cannot metabolize phenylalanine adequately, resulting in an increase in the serum levels of the amino acid (hyperphenylalaninemia). This can result in mental retardation, and also can affect the fetus of a pregnant woman who has the disorder.

Passage in 1958 of the Food Additives Amendment to the Food, Drug, and Cosmetic Act produced a major change in how food additives are regulated by the federal government. For one thing, no new food additive may be used if animal feeding studies or other appropriate tests showed that it caused cancer. This is the now-famous Delaney Clause. The *amount* of the substance one would have to consume to induce cancer is not of significance under the Delaney Clause.

Another critical feature of the 1958 amendment, however, was that it did not apply to additives that were generally recognized by experts as safe for their intended uses. Saccharin, cyclamate and a long list of other substances were being used in foods before the amendment's passage and were considered "generally recognized as safe"—or what is known today as GRAS. Aspartame, on the other hand, became the first artificial sweetener to fall under the 1958 amendment's requirement for pre-marketing proof of safety because the first petition to FDA for its approval was filed in 1973. In 1968, the Committee on Food Protection of the National Academy of Sciences issued an interim report on the safety of non-nutritive sweeteners, including saccharin. In the early 1970s, FDA began a major review of hundreds of food additives on the GRAS list to determine whether more current studies still justified their safe status. In 1972, with new studies under way, FDA decided to take saccharin off the GRAS and establish interim limits that would permit its continued use until additional studies were completed. (Previous studies indicated that male and female rats fed doses of saccharin developed a significant incidence of bladder tumors.) In November 1977, Congress passed the Saccharin Study and Labeling Act, which permitted saccharin's continued availability while mandating that warning labels be used to advise consumers that saccharin caused cancer in animals. The law also directed FDA to arrange further studies of carcinogens and toxic substances in foods.

Cyclamate was introduced into beverages and

foods in the 1950s and dominated the artificial sweetener market in the 1960s. After much controversy regarding the substance's safety, the FDA issued a final ruling in 1980 stating that the agent's safety has not been demonstrated. Since that date, scientific studies have continued in order to conclusively support or refute the basis for the FDA decision. At question is the agent's possible carcinogenicity and its possible effects in causing genetic damage and testicular atrophy. The student is referred to the indicated references for a review of the recent history of sweeteners including: saccharin, cyclamate, fructose, polyalcohols, sucrose, and aspartame (13–16).

Acesulfame potassium, a nonnutritive sweetener first discovered in 1967, was approved in 1992 by the FDA. It had been used previously in a number of other countries. The substance, structurally similar to saccharin, is 130 times as sweet as sucrose and is excreted unchanged in the urine. Acesulfame is more stable than aspartame at elevated temperatures and was approved by the FDA initially for use in candy, chewing gum, confectionery, and instant coffees and teas.

A relatively new sweetening agent introduced into U.S. commerce is Stevia. Stevia powder is the extract from the leaves of Stevia rebaudiana Bertoni plant. The product is natural, nontoxic, safe and about 30 times sweeter than cane sugar, or sucrose. It can be used in both hot and cold preparations. Table 3.4 compares three of the most used sweeteners in the food and drug industry.

Most large pharmaceutical manufacturers have special laboratories for the taste-testing of proposed formulations of their products. Panels of employees or interested community participants become involved in evaluating the various formulations and their assessments become the basis for the firm's flavoring decisions.

In flavoring liquid pharmaceutical products, the flavoring agent is added to the solvent or vehicle-component of the formulation in which it is most soluble or miscible. That is, water soluble flavorants are added to the aqueous component of a formulation and poorly water-soluble flavorants are added to the alcoholic or other non-aqueous solvent component of the formulation. In a hydroalcoholic or other multi-solvent system, care must be exercised to maintain the flavorant in solution. This is accomplished by maintaining a sufficient level of solvent in which the flavorant is soluble.

Coloring

Coloring agents are used in pharmaceutical preparations for purposes of esthetics. A distinction should be made between agents that have inherent color and those agents which are employed as colorants. Certain agents—sulfur (yellow), cupric sulfate (blue), ferrous sulfate (bluish green), and red mercuric iodide (vivid red)—have inherent color and are not thought of as pharmaceutical colorants in the usual sense of the term.

Although most pharmaceutical colorants in use today are of synthetic origin, a few are obtained from natural mineral and plant sources. For example, red ferric oxide is mixed in small proportions with zinc oxide powder to prepare calamine, giving the latter its characteristic pink color, which is intended to match the skin tone upon application.

The synthetic coloring agents used in pharmaceutical products were first prepared in the middle of the 19th century from principles of coal tar (*pix carbonis*), a thick, black, viscid liquid, is a by-product in the destructive distillation of coal. Its composition is extremely complex, and many of its constituents may be separated by fractional distillation. Among the products obtained are anthracene, benzene, naphtha, creosote, phenol, and pitch. About 90% of

Table 3.4.   Comparison of Sweeteners

	Sucrose	*Saccharin*	*Aspartame*
Source:	Sugar cane; sugar beet	Chemical synthesis; phthalic anhydride, a petroleum product	Chemical synthesis; methyl ester dipeptide of phenylalanine and aspartic acid
Relative sweetness:	1	300	180–200
Bitterness:	None	Moderate/strong	None
Aftertaste:	None	Moderate/strong;sometimes metallic or bitter	None
Calories:	4/g	0	4/g
Acid Stability:	Good	Excellent	Fair
Heat Stability:	Good	Excellent	Poor

the total dyes used in the products FDA regulates are synthesized from a single, colorless derivative of benzene, called aniline. These aniline dyes are also known as synthetic organic dyes or as "coal tar" dyes since aniline was originally obtained from bituminous coal. Aniline dyes today come mainly from petroleum.

Many coal-tar dyes were originally used indiscriminately in foods and beverages to enhance their appeal without regard to their toxic potential. It was only after careful scrutiny that some dyes were found to be hazardous to health due to either their own chemical nature or the impurities they carried. As more dyestuffs became available, some expert guidance and regulation was needed to ensure the safety of the public. After passage of the Food and Drug Act in 1906, the United States Department of Agriculture established regulations by which a few colorants were *permitted* or *certified* for use in certain products. Today, the use of color additives in foods, drugs, and cosmetics is regulated by the Food and Drug Administration through the provisions of the Federal Food, Drug, and Cosmetic Act of 1938, as amended in 1960 with the Color Additive Amendments. Lists of color additives *exempt* from certification and those *subject* to certification are codified into law and regulated by the FDA (17). Certified color additives are classified according to their approved use: (a) FD&C color additives, which may be used in foods, drugs, and cosmetics; (b) D&C color additives, some of which are approved for use in drugs, some in cosmetics, and some in medical devices; and (c) external D&C color additives, the use of which is restricted to external parts of the body, not including the lips or any other body surface covered by mucous membrane. Within each certification category there is a variety of basic colors and shades for coloring pharmaceuticals. One may select from a variety of FD&C, D&C, and External D&C reds, yellows, oranges, greens, blues, and violets. By selective combinations of the colorants one can create distinctive colors (Table 3.5).

As a part of the National Toxicology Program of the Department of Health and Human Services, various substances, including color additives, are studied for their toxicology and carcinogenesis. For color additives, the study protocols usually call for a two-year study in which groups of male and female mice and rats are fed diets containing various quantities of the colorant. The nonsurviving and surviving animals are examined for evidence of long-term toxicity and carcinogenesis. Five categories of evidence of carcinogenic activity are used in reporting observations: 1) "clear evidence" of carcinogenic activity; 2)"some evidence"; 3)"equiv-ocal evidence," indicating uncertainty; 4) "no evidence," indicating no observable effect; and 5)"inadequate study," for studies that cannot be evaluated because of major flaws incurred.

The certification status of the colorants is continuously reviewed, and changes are made in the list of certified colors in accordance with toxicologic findings. These changes may involve 1) the withdrawal of certification, 2) the transfer of a colorant from one certification category to another, or 3) the addition of new colors to the list. Before gaining certification, a color additive must be demonstrated to be safe. In the case of pharmaceutical preparations, color additives, like all additives, must not interfere with the therapeutic efficacy of the product in which they are used nor may they interfere with the prescribed assay procedure for that preparation.

Table 3.5.   Examples of Color Formulations*

Shade/Color	FD&C Dye	% of Blend
Orange	Yellow #6	100
	or	
	Yellow #5	95
	Red #40	5
Cherry	Red #40	100
	or	
	Red #40	99
	Blue #1	1
Strawberry	Red #40	100
	or	
	Red #40	95
	Red #3	5
Lemon	Yellow #5	100
Lime	Yellow #5	95
	Blue #1	5
Grape	Red #40	80
	Blue #1	20
Raspberry	Red #3	75
	Yellow #6	20
	Blue #1	5
Butterscotch	Yellow #5	74
	Red #40	24
	Blue #1	2
Chocolate	Red #40	52
	Yellow #5	40
	Blue #1	8
Caramel	Yellow #5	64
	Red #3	21
	Yellow #6	9
	Blue #1	6
Cinnamon	Yellow #5	60
	Red #40	35
	Blue #1	5

*From literature of Warner-Jenkinson Co., St. Louis, Mo.

In the 1970s, concern and scientific questioning of the safety of some color additives heightened. A color that drew particular attention was FD&C Red No. 2, because of its extensive use in foods, drugs and cosmetics. Researchers in Russia had reported that this color, also known as amaranth, caused cancer in rats. Although the FDA was never able to determine the purity of the amaranth tested in Russia, these reports led to FDA investigations and a series of tests that eventually resulted in withdrawal of FD&C Red No. 2 from the FDA certified list in 1976 because its sponsors were unable to prove safety. That year, the Agency also terminated approval for use of FD&C Red No. 4 in maraschino cherries and ingested drugs because of unresolved safety questions. FD&C Red No. 4 is now permitted only in externally applied drugs and cosmetics.

The dye FD&C Yellow No. 5 (also known as tartrazine) can cause many people to have allergic-type reactions. People who are allergic to aspirin will also likely be allergic to this dye. As a result, the FDA requires the listing of this dye by name on the labels of foods (e.g., butter, cheese, ice cream) and ingested drugs containing the substance.

A colorant becomes an integral part of a pharmaceutical formulation, and its exact quantitative amount must be reproducible each time the formulation is prepared, or else the preparation would have a different appearance from batch to batch. This requires a high degree of pharmaceutical skill, for the amount of colorant generally added to liquid preparations ranges between 0.0005 and 0.001% depending upon the colorant and the depth of color desired. Because of their color potency, dyes generally are added to pharmaceutical preparations in the form of diluted solutions rather than as concentrated dry powders. This permits greater accuracy in measurement and more consistent color production.

In addition to liquid dyes in the coloring of pharmaceuticals, lake pigments may also be used. Whereas a chemical material exhibits coloring power or tinctorial strength when dissolved, pigment is an insoluble material which colors by dispersion. An FD&C lake is a pigment consisting of a substratum of alumina hydrate on which the dye is absorbed or precipitated. Having aluminum hydroxide as the substrate, the lakes are insoluble in nearly all solvents. FD&C lakes are subject to certification and must be made from dyes which have been previously certified. Lakes do not have a specified dye content and range from 10 to 40% pure dye. By their very nature, lakes are suitable for coloring products in which the moisture levels are low.

Lakes are commonly used in the form of fine dispersions or suspensions when coloring pharmaceuticals. The pigment particles may range in size from less than 1 μm up to 30 μm. The finer the particle, the less chance there would be for color speckling to occur in the finished product. Blends of various lake pigments may be used to achieve a variety of colors and different vehicles may be employed to disperse the colorants, as glycerin, propylene glycol, and sucrose-based syrup.

In the preparation of capsules, various colored empty gelatin capsule shells may be used to hold the powdered drug mixture. Many commercial capsules are prepared with capsule bodies of one color and a different colored capsule cap, resulting in a two-colored capsule. This makes certain commercial products even more readily identifiable than solid colored capsules. For powdered drugs dispensed as such or compressed into tablets, a generally larger proportion of dye is required (about 0.1%) to achieve the desired hue than with liquid preparations.

Both dyes and lakes have application in the coloring of sugar-coated tablets, film-coated tablets, direct-compression tablets, pharmaceutical suspensions and other dosage forms (18). Traditionally, sugar-coated tablets have been colored with syrup solutions containing varying amounts of the water-soluble dyes, starting with very dilute solutions, working up to concentrated color syrup solutions. As many as 30 to 60 coats are not uncommon. Using the FD&C lakes, fewer color coats are used. Appealing tablets have been made with as few as 8 to 12 coats using lakes dispersed in syrup. Water-soluble dyes in aqueous vehicles or lakes dispersed in organic solvents may be effectively sprayed on tablets to achieve attractive film coatings. There is continued interest today in chewable tablets, due to the availability of many direct-compression materials such as dextrose, sucrose, mannitol, sorbitol, and spray-dried lactose. The direct-compression colored chewable tablets may be prepared utilizing 1 pound of lake per 1000 pounds of tablet mix. For aqueous suspensions, FD&C water-soluble colors or lakes may be satisfactory. In non-aqueous suspensions, FD&C lakes are necessary. The lakes, added either to the aqueous or non-aqueous phase, generally at a level of 1 pound of color per 1000 pounds of suspension, require homogenizing or mechanical blending to achieve uniform coloring.

For the most part, ointments, suppositories, and ophthalmic and parenteral products assume the color of their ingredients and do not contain color additives. Should a dye lose the certification status it held when a product was first formulated, manufactured, and marketed, the manufacturer must,

within a reasonable length of time, reformulate, using only color additives certified at the new date of manufacture.

In addition to esthetics and the certification status of a dye, a formulation pharmacist must select the dyes to be used in a particular formula on the basis of the physical and chemical properties of the dyes available. Of prime importance is the solubility of a prospective dye in the vehicle to be used for a liquid formulation or in a solvent to be employed during a pharmaceutical process, as when the dye is sprayed on a batch of tablets. In general, most dyes are broadly grouped into those that are water-soluble and those that are oil-soluble; few, if any, dyes are both. Usually, a water-soluble dye is also adequately soluble in commonly used pharmaceutical liquids like glycerin, alcohol, and glycol ethers. Oil-soluble dyes may also be soluble to some extent in these solvents, as well as in liquid petrolatum (mineral oil), fatty acids, fixed oils, and waxes. It should be remembered that a great deal of solubility is not required, since the concentration of dye in a given preparation is rather minimal.

Another important consideration when selecting a dye for use in a liquid pharmaceutical is the pH and pH stability of the preparation to be colored. Dyes can change color with a change in pH, and a dye must be selected for a product so that any anticipated pH change will not alter the color during the usual shelf-life. The dye also must be chemically stable in the presence of the other formulative ingredients and must not interfere with the stability of the other agents. To maintain their original colors, FD&C dyes must be protected from oxidizing agents, reducing agents (especially metals as iron, aluminum, zinc and tin), strong acids and alkalis, and excessive heating. Dyes must also be reasonably photostable; that is, they must not change color when exposed to light of anticipated intensities and wavelengths under the usual conditions of shelf storage. Certain medicinal agents, particularly those prepared in liquid form, must be protected from light to maintain their chemical stability and their therapeutic effectiveness. These preparations are generally maintained and dispensed in dark amber or opaque containers. For solid dosage forms of photolabile drugs, a colored or opaque capsule shell may actually enhance the drug's stability by shielding out light rays.

Preservatives

In addition to the stabilization of pharmaceutical preparations against chemical and physical degradation due to changed environmental conditions within a formulation, certain liquid and semisolid preparations also must be preserved against microbial contamination.

Sterilization and Preservation

Although some types of pharmaceutical products like ophthalmic and injectable preparations are sterilized by physical methods (autoclaving for 20 minutes at 15 pounds pressure and 120°C, dry heat at 180°C for 1 hour, or by bacterial filtration) during their manufacture, many of them additionally require the presence of an antimicrobial preservative to maintain their aseptic condition throughout the period of their storage and use. Other types of preparations that are not sterilized during their preparation but are particularly susceptible to microbial growth because of the nature of their ingredients, are protected by the addition of an antimicrobial preservative. Preparations that provide excellent growth media for microbes are most aqueous preparations, especially syrups, emulsions, suspensions, and some semisolid preparations, particularly creams. Certain hydroalcoholic and most alcoholic preparations may not require the addition of a chemical preservative when the alcoholic content is sufficient to prevent microbial growth. Generally, 15% alcohol will prevent microbial growth in acid media and 18% in alkaline media. Most alcohol-containing pharmaceuticals such as elixirs, spirits, and tinctures are self-sterilizing and do not require additional preservation. The same would apply to other pharmaceuticals on an individual basis, which by virtue of their vehicles or other formulative agents, may not permit the growth of microorganisms.

Preservative Selection

When experience or shelf-storage experiments indicate that a preservative is required in a pharmaceutical preparation, its selection is based on many cross considerations including some of the following.

1. The preservative prevents the growth of the type of microorganisms considered the most likely contaminants of the preparation being formulated.
2. The preservative is soluble enough in water to achieve adequate concentrations in the aqueous phase of a two or more phase system.
3. The proportion of preservative remaining undissociated at the pH of the preparation makes it capable of penetrating the microorganisms and destroying its integrity.

4. The required concentration of the preservative does not affect the safety or comfort of the patient when the pharmaceutical preparation is administered by the usual or intended route; i.e., nonirritating, nonsensitizing, nontoxic.
5. The preservative has adequate stability and will not be reduced in concentration due to chemical decomposition or volatilization during the desired shelf-life of the preparation.
6. The preservative is completely compatible with all other formulative ingredients and does not interfere with them, nor do they interfere with the effectiveness of the preservative agent.
7. The preservative does not adversely affect the preparation's container or the closure.

General Preservative Considerations

Microorganisms involved include molds, yeasts, and bacteria, with the latter generally favoring a slightly alkaline medium and the others an acid medium. Although few microorganisms can grow below a pH of 3 or above pH 9, most aqueous pharmaceutical preparations are within the favorable pH range and therefore must be protected against microbial growth. To be effective, a preservative agent must be dissolved in sufficient concentration in the aqueous phase of a preparation. Further, only the undissociated fraction or molecular form of a preservative possesses preservative capability, because the ionized portion is incapable of penetrating the microorganism. Thus the preservative selected must be largely undissociated at the pH of the formulation being prepared. Acidic preservatives like benzoic, boric, and sorbic acids are more undissociated and thus more effective as the medium is made more acid. Conversely, alkaline preservatives are less effective in acid or neutral media and more effective in alkaline media. Thus, it is meaningless to suggest preservative effectiveness at specific concentrations unless the pH of the system is mentioned and the undissociated concentration of the agent is calculated or otherwise determined. Also, if formulative materials interfere with the solubility or availability of the preservative agent, its chemical concentration may be misleading, because it may not be a true measure of the effective concentration. Many incompatible combinations of preservative agents and other pharmaceutical adjuncts have been discovered in recent years, and undoubtedly many more will be uncovered in the future as new preservatives, pharmaceutical adjuncts, and therapeutic agents are combined for the first time. Many of the

recognized incompatible combinations that result in preservative inactivation involve macromolecules such as various cellulose derivatives, polyethylene glycols, and natural gums such as tragacanth, which can attract and hold preservative agents, such as the parabens and phenolic compounds, rendering them unavailable for their preservative function. It is essential for the research pharmacist to examine all formulative ingredients as one affects the other to assure himself that each agent is free to do the job for which it was included in the formulation. In addition, the preservative must not interact with a container such as a metal ointment tube or a plastic medication bottle or with an enclosure such as a rubber or plastic cap or liner. Such an interaction could result in the decomposition of the preservative or the container closure, or, both, with resultant product decomposition and contamination. Appropriate tests should be devised and conducted to insure against this type of preservative interaction.

Mode of Action

Preservatives interfere with microbial growth, multiplication, and metabolism through one or more of the following mechanisms:

1. Modification of cell membrane permeability and leakage of cell constituents (partial lysis)
2. Lysis and cytoplasmic leakage
3. Irreversible coagulation of cytoplasmic constituents (e.g., protein precipitation)
4. Inhibition of cellular metabolism as through interference with enzyme systems or inhibition of cell wall synthesis
5. Oxidation of cellular constituents
6. Hydrolysis

A few of the commonly used pharmaceutical preservatives and their probable modes of action are presented in Table 3.6.

Preservative Utilization

Suitable substances may be added to a pharmaceutical preparation to enhance its permanency or usefulness. Such additives are suitable only if they are nontoxic and harmless in the amounts administered and do not interfere with the therapeutic efficacy or tests or assays of the preparation. Certain intravenous preparations given in large volumes as blood replenishers or as nutrients are not permitted to contain bacteriostatic additives, because the amounts required to preserve such large volumes would constitute a health hazard when administered to the patient. Thus preparations

Table 3.6.   Probable Modes of Action of Some Preservatives

Preservative	Probable Modes of Action
Benzoic acid, boric acid, and p-hydroxybenzoates	Denaturation of proteins
Phenols and chlorinated phenolic compounds	Lytic and denaturation action on cytoplasmic membranes and for chlorinated preservatives, also by oxidation of enzymes
Alcohols	Lytic and denaturation action on membranes
Quaternary compounds	Lytic action on membranes
Mercurials	Denaturation of enzymes by combining with thiol (-SH) groups)

like Dextrose Injection, USP, and others commonly given as fluid and nutrient replenishers by intravenous injections in amounts of 500 to 1000 mL may not contain antibacterial preservatives. On the other hand, injectable preparations given in small volumes—for example, Morphine Sulfate Injection, USP, which provides a therapeutic amount of morphine sulfate in approximately a 1-mL volume— can be preserved with a suitable preservative without the danger of coadministering an excessive amount of the preservative to the patient.

Examples of the preservatives and their concentrations commonly employed in pharmaceutical preparations are: benzoic acid (0.1 to 0.2%), sodium benzoate (0.1 to 0.2%), alcohol (15 to 20%), phenylmercuric nitrate and acetate (0.002 to 0.01%), phenol (0.1 to 0.5%), cresol (0.1 to 0.5%), chlorobutanol (0.5%), benzalkonium chloride (0.002 to 0.01%), and combinations of methylparaben and propylparaben (0.1 to 0.2%), the latter being especially good against fungus. The required proportion would vary with the factors of pH, dissociation, and others already indicated as well with the presence of other formulative ingredients with inherent preservative capabilities that contribute to the preservation of the preparation and require less additional preservation assistance.

For each type of preparation to be preserved, the research pharmacist must consider the influence of the preservative on the comfort of the patient. For instance, a preservative in an ophthalmic preparation would have to have an extremely low degree of irritant qualities, which is characteristic of chlorobutanol, benzalkonium chloride, and phenylmercuric nitrate, frequently used preservatives in ophthalmic preparations. In all instances, the preserved preparation must be biologically tested to determine its safety and efficacy and shelf-tested to determine its stability for the intended shelf life of the product.

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4

DOSAGE FORM DESIGN: BIOPHARMACEUTIC AND PHARMACOKINETIC CONSIDERATIONS

Chapter at a Glance

AS DISCUSSED in the previous chapter, the biologic response to a drug is the result of an interaction between the drug substance and functionally important cell receptors or enzyme systems. The response is due to an alteration in the biologic processes that were present prior to the drug's administration. The magnitude of the response is related to the concentration of the drug achieved at the site of its ac-

tion. This drug concentration depends on the dosage of the drug administered, the extent of its absorption and distribution to the site, and the rate and extent of its elimination from the body. The physical and chemical constitution of the drug substance—particularly its lipid solubility, degree of ionization, and molecular size—determines to a great extent its ability to effect its biological activity. The area of

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study embracing this relationship between the physical, chemical, and biological sciences as they apply to drugs, dosage forms, and to drug action has been given the descriptive term *biopharmaceutics*.

In general, for a drug to exert its biologic effect, it must be transported by the body fluids, traverse the required biologic membrane barriers, escape widespread distribution to unwanted areas, endure metabolic attack, penetrate in adequate concentration to the sites of action, and interact in a specific fashion, causing an alteration of cellular function. A simplified diagram of this complex series of events between a drug's administration and its elimination is presented in Figure 4.1.

The absorption, distribution, biotransformation (metabolism), and elimination of a drug from the body are dynamic processes that continue from the time a drug is taken until all of the drug has been removed from the body. The *rates* at which these processes occur affect the onset, intensity, and the duration of the drug's activity within the body. The area of study which elucidates the time course of drug concentration in the blood and tissues is termed *pharmacokinetics*. It is the study of the kinetics of absorption, distribution, metabolism and excretion (ADME) of drugs and their corresponding pharmacologic, therapeutic, or toxic response in animals and man. Further, since one drug may alter the absorption, distribution, metabolism or excretion of another drug, pharmacokinetics also may be applied in the study of interactions between drugs.

Once a drug is administered and drug absorption begins, the drug does not remain in a single body location, but rather is distributed throughout the body until its ultimate elimination. For instance, following the oral administration of a drug and its entry into the gastrointestinal tract, a por-
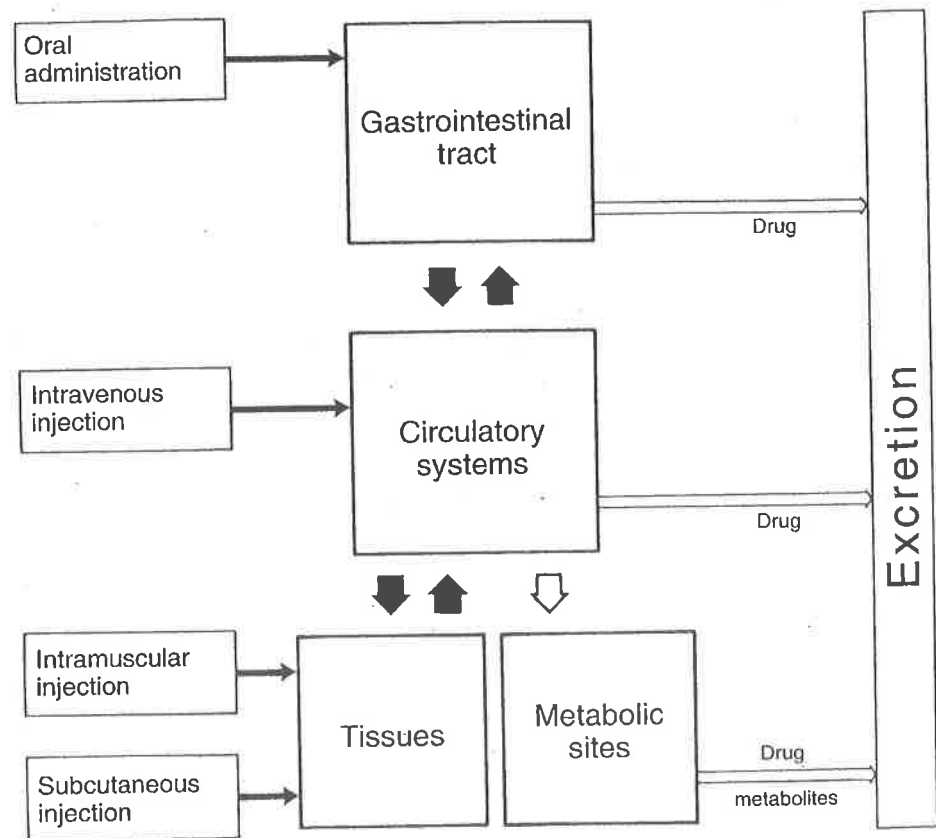

Fig. 4.1 *Schematic representation of events of absorption, metabolism, and excretion of drugs after their administration by various routes.*

tion of the drug is absorbed into the circulatory system from which it is distributed to the various other body fluids, tissues, and organs. From these sites the drug may return to the circulatory system and be excreted through the kidney as such or the drug may be metabolized by the liver or other cellular sites and be excreted as metabolites. As shown in Figure 4.1, drugs administered by intravenous injection are placed directly into the circulatory system, thereby avoiding the absorption process, which is required from all other routes of administration for systemic effects.

The various body locations to which a drug travels may be viewed as separate compartments, each containing some fraction of the administered dose of drug. The transfer of drug from the blood to other body locations is generally a rapid process and is reversible; that is, the drug may diffuse back into the circulation. The drug in the blood therefore exists in equilibrium with the drug in the other compartments. However, in this equilibrium state, the concentration of the drug in the blood may be quite different (greater or lesser) than the concentration of the drug in the other compartments. This is due largely to the physiochemical properties of the drug and its resultant ability to leave the blood and traverse the biological membranes. Certain drugs may leave the circulatory system rapidly and completely, whereas other drugs may do so slowly and with difficulty. A number of drugs become bound to blood proteins, particularly the albumins, and only a small fraction of the drug administered may actually be found at locations outside of the circulatory system at a given time. The transfer of drug from one compartment to another is mathematically associated with a specific rate constant describing that particular transfer. Generally, the rate of transfer of a drug from one compartment to another is proportional to the concentration of the drug in the compartment from which it exits; the greater the concentration, the greater is the amount of drug transfer.

Metabolism is the major process by which foreign substances, including drugs are eliminated from the body. In the process of metabolism a drug substance may be biotransformed into pharmacologically active or inactive metabolites. Often, both the drug substance and its metabolite(s) are active and exert pharmacologic effects. For example, the antianxiety drug prazepam (Centrax) metabolizes, in part, to oxazepam (Serax), which also has antianxiety effects. In some instances a pharmacologically inactive drug (termed a *prodrug*) may be administered for the known effects of its active metabolites. Dipivefrin,

for example, is a prodrug of epinephrine formed by the esterification of epinephrine and pivalic acid. This enhances the lipophilic character of the drug, and as a consequence its penetration into the anterior chamber of the eye is 17 times that of epinephrine. Within the eye, dipivefrin HCl is converted by enzymatic hydrolysis to epinephrine.

The metabolism of a drug to inactive products is usually an irreversible process which culminates in the excretion of the drug from the body, usually via the urine. The pharmacokineticist may calculate an elimination rate constant (termed k_{el}) for a drug to describe its rate of elimination from the body. The term *elimination* refers to both metabolism and excretion. For drugs that are administered intravenously, and therefore involve no absorption process, the task is much less complex than for drugs administered orally or by other routes. In the latter instances, drug absorption and drug elimination are occurring simultaneously but at different rates.

General Principles of Drug Absorption

Before an administered drug can arrive at its site of action in effective concentrations, it must surmount a number of barriers. These barriers are chiefly a succession of biologic membranes such as those of the gastrointestinal epithelium, lungs, blood, and brain. Body membranes are generally classified as three main types: (a) those composed of several layers of cells, as the skin; (b) those composed of a single layer of cells, as the intestinal epithelium; and (c) those of less than one cell in thickness, as the membrane of a single cell. In most instances a drug substance must pass more than one of these membrane types before it reaches its site of action. For instance, a drug taken orally must first traverse the gastrointestinal membranes (stomach, small and large intestine), gain entrance into the general circulation, pass to the organ or tissue with which it has affinity, gain entrance into that tissue, and then enter into its individual cells.

Although the chemistry of body membranes differs one from another, the membranes may be viewed in general as a bimolecular lipoid (fat-containing) layer attached on both sides to a protein layer. Drugs are thought to penetrate these biologic membranes in two general ways: 1) by passive diffusion, and 2) through specialized transport mechanisms. Within each of these main categories, more clearly defined processes have been ascribed to drug transfer.

Passive Diffusion

The term *passive diffusion* is used to describe the passage of (drug) molecules through a membrane which behaves inertly in that it does not actively participate in the process. Drugs absorbed according to this method are said to be *passively absorbed*. The absorption process is driven by the concentration gradient (i.e., the differences in concentration) existing across the membrane, with the passage of drug molecules occurring primarily from the side of high drug concentration. Most drugs pass through biologic membranes by diffusion.

Passive diffusion is described by *Fick's first law*, which states that the rate of diffusion or transport across a membrane (dc/dt) is proportional to the difference in drug concentration on both sides of the membrane:

$$-\frac{dc}{dt} = P(C_1 - C_2)$$

in which C_1 and C_2 refer to the drug concentrations on each side of the membrane and P is a permeability coefficient or constant. The term C_1 is customarily used to represent the compartment with the greater concentration of drug and thus the transport of drug proceeds from compartment one (e.g., absorption site) to compartment two (e.g., blood).

Because the concentration of drug at the site of absorption (C_1) is usually much greater than on the other side of the membrane, due to the rapid dilution of the drug in the blood and its subsequent distribution to the tissues, for practical purposes the value of $C_1 - C_2$ may be taken simply as that of C_1 and the equation written in the standard form for a first order rate equation:

$$-\frac{dc}{dt} = PC_1$$

The gastrointestinal absorption of most drugs from solution occurs in this manner in accordance with *first order kinetics* in which the rate is dependent on drug concentration, i.e., doubling the dose doubles the transfer rate. The magnitude of the permeability constant, depends on the diffusion coefficient of the drug, the thickness and area of the absorbing membrane, and the permeability of the membrane to the particular drug.

Because of the lipoid nature of the cell membrane, it is highly permeable to lipid soluble substances. The rate of diffusion of a drug across the membrane depends not only upon its concentration but also upon the relative extent of its affinity for lipid and rejection of water (a high lipid partition coefficient). The greater its affinity for lipid and the more hydrophobic it is, the faster will be its rate of penetration into the lipid-rich membrane. Erythromycin base, for example, possesses a higher partition coefficient than other erythromycin compounds, e.g., estolate, gluceptate. Consequently, the base is the preferred agent for the topical treatment of acne where penetration into the skin is desired.

Because biologic cells are also permeated by water and lipid-insoluble substances, it is thought that the membrane also contains water-filled pores or channels that permit the passage of these types of substances. As water passes in bulk across a porous membrane, any dissolved solute molecularly small enough to traverse the pores passes in by *filtration*. Aqueous pores vary in size from membrane to membrane and thus in their individual permeability characteristics for certain drugs and other substances.

The majority of drugs today are weak organic acids or bases. Knowledge of their individual ionization or dissociation characteristics is important, because their absorption is governed to a large extent by their degrees of ionization as they are presented to the membrane barriers. Cell membranes are more permeable to the unionized forms of drugs than to their ionized forms, mainly because of the greater lipid solubility of the unionized forms and to the highly charged nature of the cell membrane which results in the binding or repelling of the ionized drug and thereby decreases cell penetration. Also, ions become hydrated through association with water molecules, resulting in larger particles than the undissociated molecule and again decreased penetrating capability.

The degree of a drug's ionization depends both on the pH of the solution in which it is presented to the biologic membrane and on the pK_a, or dissociation constant, of the drug (whether an acid or base). The concept of pK_a is derived from the Henderson-Hasselbalch equation and is:

For an acid:

$$pH = pK_a + \log\frac{\text{ionized conc. (salt)}}{\text{unionized conc. (acid)}}$$

For a base:

$$pH = pK_a + \log\frac{\text{unionized conc. (base)}}{\text{ionized conc. (salt)}}$$

Since the pH of body fluids varies (stomach, pH 1; lumen of the intestine, pH 6.6; blood plasma, pH 7.4), the absorption of a drug from various body fluids will differ and may dictate to some extent the type of dosage form and the route of administration preferred for a given drug.

By rearranging the equation for an acid:

$$pK_a - pH = \log \frac{\text{unionized concentration (acid)}}{\text{ionized concentration (salt)}}$$

one can theoretically determine the relative extent to which a drug remains unionized under various conditions of pH. This is particularly useful when applied to conditions of body fluids. For instance, if a weak acid having a pK_a of 4 is assumed to be in an environment of gastric juice with a pH of 1, the left side of the equation would yield the number 3, which would mean that the ratio of unionized to ionized drug particles would be about 1000 to 1, and gastric absorption would be excellent. At the pH of plasma the reverse would be true, and in the blood the drug would be largely in the ionized form. Table 4.1 presents the effect of pH on the ionization of weak electrolytes, and Table 4.2 offers some representative pK_a values of common drug substances.

From the equation and from Table 4.1, it may be seen that a drug substance is half ionized at a pH which is equal to its pK_a. Thus pK_a may be defined as the pH at which a drug is 50% ionized. For example, phenobarbital has a pK_a value of about 7.4, and in plasma (pH 7.4) it is present as ionized and unionized forms in equal amounts. However, a drug substance cannot reach the blood plasma for distribution throughout the body unless it is placed there directly through intravenous injection or is favorably absorbed from a site along its route of entry, as the gastrointestional tract, and allowed to pass into the general circulation. As shown in Table 4.2, phenobarbital, a weak acid, with a pK_a of 7.4 would

Table 4.1. The Effect of pH on the Ionization of Weak Electrolytes* pK_a-pH % Unionized

	If Weak Acid	If Weak Base
−3.0	0.100	99.9
−2.0	0.990	99.0
−1.0	9.09	90.9
−0.7	16.6	83.4
−0.5	24.0	76.0
−0.2	38.7	61.3
0	50.0	50.0
+0.2	61.3	38.7
+0.5	76.0	24.0
+0.7	83.4	16.6
+1.0	90.9	9.09
+2.0	99.0	0.990
+3.0	99.9	0.100

*Reprinted with permission from Doluisio JT, Swintosky JV. Am J Pharm 1965;137:149.

Table 4.2. pK_a Values for Some Acidic and Basic Drugs

		pK_a
Acids:	Acetylsalicylic acid	3.5
	Barbital	7.9
	Benzylpenicillin	2.8
	Boric acid	9.2
	Dicoumarol	5.7
	Phenobarbital	7.4
	Phenytoin	8.3
	Sulfanilamide	10.4
	Theophylline	9.0
	Thiopental	7.6
	Tolbutamide	5.5
	Warfarin	4.8
Bases:	Amphetamine	9.8
	Apomorphine	7.0
	Atropine	9.7
	Caffeine	0.8
	Chlordiazepoxide	4.6
	Cocaine	8.5
	Codeine	7.9
	Guanethidine	11.8
	Morphine	7.9
	Procaine	9.0
	Quinine	8.4
	Reserpine	6.6

be largely undissociated in the gastric environment of pH 1 and would likely be well absorbed. A drug may enter the circulation rapidly and at high concentrations if membrane penetration is easily accomplished or at a low rate and low level if the drug is not readily absorbed from its route of entry. The pH of the drug's current environment influences the rate and the degree of its further distribution because it becomes more or less unionized and therefore more or less lipid-penetrating under some condition of pH than under another. If an unionized molecule is able to diffuse through the lipid barrier and remain unionized in the new environment, it may return to its former location or go on to a new one. However, if in the new environment it is greatly ionized due to the influence of the pH of the second fluid, it likely will be unable to cross the membrane with its former ability. Thus a concentration gradient of a drug usually is reached at equilibrium on each side of a membrane due to different degrees of ionization occurring on each side. A summary of the concepts of dissociation/ionization is found in the physical pharmacy capsule entitled "pKa/Dissociation Constants" in Chapter 3.

It is often desirable for pharmaceutical scientists to make structural modifications in organic drugs

and thereby favorably alter their lipid solubility, partition coefficients, and dissociation constants while maintaining the same basic pharmacologic activity. These efforts frequently result in increased absorption, better therapeutic response, and lower dosage.

Specialized Transport Mechanisms

In contrast to the passive transfer of drugs and other substances across a biologic membrane, certain substances, including some drugs and biologic metabolites, are conducted across a membrane through one of several postulated *specialized transport* mechanisms. This type of transfer seems to account for those substances, many naturally occurring as amino acids and glucose, that are too lipid-insoluble to dissolve in the boundary and too large to flow or filter through the pores. This type of transport is thought to involve membrane components that may be enzymes or some other type of agent capable of forming a complex with the drug (or other agent) at the surface membrane, after which the complex moves across the membrane where the drug is released, with the carrier returning to the original surface. Figure 4.2 presents the simplified scheme of this process. Specialized transport may be differentiated from passive transfer in that the former process may become "saturated" as the amount of carrier present for a given substance becomes completely bound with that substance resulting in a delay in the "ferrying" or transport process. Other features of specialized transport include the specificity by a 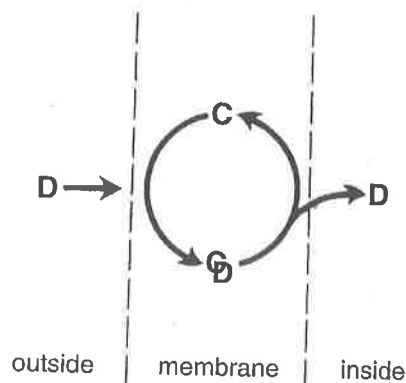carrier for a particular type of chemical structure so that if two substances are transported by the same mechanism one will competitively inhibit the transport of the other. Further, the transport mechanism is inhibited in general by substances that interfere with cell metabolism. The term *active transport*, as a subclassification of specialized transport, denotes a process with the additional feature of the solute or drug being moved across the membrane against a concentration gradient, that is, from a solution of lower concentration to one of a higher concentration or, if the solute is an ion, against an electrochemical potential gradient. In contrast to active transport, *facilitated diffusion* is a specialized transport mechanism having all of the above characteristics except that the solute is not transferred against a concentration gradient and may attain the same concentration inside the cell as that on the outside.

Many body nutrients, as sugars and amino acids, are transported across the membranes of the gastrointestinal tract by carrier processes. Certain vitamins, as thiamine, niacin, riboflavin and vitamin B_6, and drug substances as methyldopa and 5-fluorouracil, require active transport mechanisms for their absorption.

Investigations of intestinal transport have often utilized *in situ* (at the site) or *in vivo* (in the body) animal models or *ex vivo* (outside the body) transport models; however, recently cell culture models of human small-intestine absorptive cells have become available to investigate transport across intestinal epithelium (1). Both passive and transport-mediated studies have been conducted to investigate mechanisms as well as rates of transport.

Fig. 4.2   *Active transport mechanism. D represents a drug molecule; C represents the carrier in the membrane. (Modified from O'Reilly W. Aust J Pharm 1966;47:568.)*

Dissolution and Drug Absorption

For a drug to be absorbed, it must first be dissolved in the fluid at the absorption site. For instance, a drug administered orally in tablet or capsule form cannot be absorbed until the drug particles are dissolved by the fluids at some point within the gastrointestinal tract. In instances in which the solubility of a drug is dependent upon either an acidic or basic medium, the drug would be dissolved in the stomach or intestines respectively (Fig. 4.3). The process by which a drug particle dissolves is termed *dissolution*.

As a drug particle undergoes dissolution, the drug molecules on the surface are the first to enter into solution creating a saturated layer of drug-solution which envelops the surface of the solid drug particle. This layer of solution is referred to as the *diffusion layer*. From this diffusion layer, the
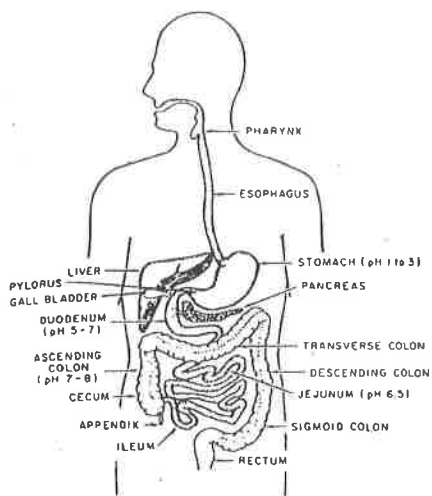
Fig. 4.3 *Anatomical diagram showing the digestive system including the locations involved in drug absorption and their respective pH values.*

drug molecules pass throughout the dissolving fluid and make contact with the biologic membranes and absorption ensues. As the molecules of drug continue to leave the diffusion layer, the layer is replenished with dissolved drug from the surface of the drug particle and the process of absorption continues.

If the process of dissolution for a given drug particle is rapid, or if the drug is administered as a solution and remains present in the body as such, the rate at which the drug becomes absorbed would be primarily dependent upon its ability to traverse the membrane barrier. However, if the rate of dissolution for a drug particle is slow, as may be due to the physiochemical characteristics of the drug substance or the dosage form, the dissolution process itself would be a rate-limiting step in the absorption process. Slowly soluble drugs such as digoxin, may not only be absorbed at a slow rate, they may be incompletely absorbed, or, in some cases largely unabsorbed following oral administration, due to the natural limitation of time that they may remain within the stomach or the intestinal tract. Thus, poorly soluble drugs or poorly formulated drug products may result in a drug's incomplete absorption and its passage, unchanged, out of the system via the feces.

Under normal circumstances a drug may be expected to remain in the stomach for 2 to 4 hours (*gastric emptying time*) and in the small intestines

for 4 to 10 hours, although there is substantial variation between people, and even in the same person on different occasions. Various techniques have been used to determine gastric emptying time and the gastrointestinal passage of drug from various oral dosage forms, including the tracking of dosage forms labeled with gamma-emitting radionuclides through gamma scintigraphy (2, 3). The gastric emptying time for a drug is most rapid with a fasting stomach, becoming slower as the food content is increased. Changes in gastric emptying time and/or in intestinal motility can affect drug transit time and thus the opportunity for drug dissolution and absorption.

These changes can be affected by drugs the patient may be taking. Certain drugs with anticholinergic properties, e.g., dicyclomine HCl, amitriptyline HCl, have the ability to slow down gastric emptying. This can enhance the rate of absorption of drugs normally absorbed from the stomach, and reduce the rate of absorption of drugs that are primarily absorbed from the small intestine. Alternatively, drugs which enhance gastric motility, e.g., laxatives, may cause some drugs to move so quickly through the gastrointestinal system and past their absorptive site at such a rate to reduce the amount of drug actually absorbed. This effect has been demonstrated with digoxin, whose absorption is significantly decreased by accelerating gastrointestinal motility.

The aging process itself may also influence gastrointestinal absorption. In the elderly, gastric acidity, the number of absorptive cells, intestinal blood flow, the rate of gastric emptying and intestinal motility are all decreased. However, drugs in which absorption depends on passive processes are not affected by these factors as much as those that depend on active transport mechanisms, e.g., calcium, iron, thiamine, and sugars. A decrease in gastric emptying time would be advantageous for those drugs that are absorbed from the stomach but disadvantageous for those drugs which are prone to acid degradation, e.g., penicillins, erythromycin, or inactivated by stomach enzymes, e.g., L-dopa.

The dissolution of a substance may be described by the modified Noyes-Whitney equation:

$$\frac{dc}{dt} = kS(c_s - c_t)$$

in which dc/dt is the rate of dissolution, k is the dissolution rate constant, S is the surface area of the dissolving solid, c_s is the saturation concentration of drug in the diffusion layer (which may be approximated by the maximum solubility of the drug

in the solvent since the diffusion layer is considered saturated), and c_t is the concentration of the drug in the dissolution medium at time t ($c_s - c_t$ is the concentration gradient). The rate of dissolution is governed by the rate of diffusion of solute molecules through the diffusion layer into the body of the solution. The equation reveals that the dissolution rate of a drug may be increased by increasing the surface area (reducing the particle size) of the drug, by increasing the solubility of the drug in the diffusion layer, and by factors embodied in the dissolution rate constant, k, including the intensity of agitation of the solvent and the diffusion coefficient of the dissolving drug. For a given drug, the diffusion coefficient and usually the concentration of the drug in the diffusion layer will increase with increasing temperature. Also, increasing the rate of agitation of the dissolving medium will increase the rate of dissolution. A reduction in the viscosity of the solvent employed is another means which may be used to enhance the dissolution rate of a drug. Changes in the pH or the nature of the solvent which influence the solubility of the drug may be used to advantage in increasing dissolution rate. Effervescent, buffered aspirin tablet formulations use some of these principles to their advantage. Due to the alkaline adjuvants in the tablet, the solubility of the aspirin is enhanced within the diffusional layer and the evolution of carbon dioxide agitates the solvent system, i.e., gastric juices. Consequently, the rate of aspirin absorbed into the bloodstream is faster than that achieved from a conventional aspirin tablet formulation. If this dosage form is acceptable to the patient, it provides a quicker means for the patient to gain relief from a troublesome headache. Many manufacturers will utilize a particular amorphous, crystalline, salt or ester form of a drug that will exhibit the solubility characteristics needed to achieve the desired dissolution characteristics when administered. Some of these factors that affect drug dissolution briefly are discussed in the following paragraphs, whereas others will be discussed in succeeding chapters in which they are relevant.

The chemical and physical characteristics of a drug substance that can affect drug/drug product safety, efficacy, and stability must be carefully defined by appropriate standards in an application for FDA approval and then substained and controlled throughout product manufacture.

Surface Area

When a drug particle is reduced to a larger number of smaller particles, the total surface area created is increased. For drug substances that are poorly or slowly soluble, this generally results in an increase in the *rate* of dissolution. This is explained in the Physical Pharmacy Capsule, "Particle Size, Surface Area and Dissolution Rate."

Increased therapeutic response to orally administered drugs due to smaller particle size has been reported for a number of drugs, among them theophylline, a xanthine derivative used to treat bronchial asthma; griseofulvin, an antibiotic with antifungal activity; sulfisoxazole, an anti-infective sulfonamide, and nitrofurantoin, a urinary anti-infective drug. To achieve increased surface area, pharmaceutical manufacturers frequently use *micronized* powders in their solid dosage form products. Micronized powders consist of drug particles reduced in size to about 5 microns and smaller. A slight variation on this is accomplished by blending and melting the poorly water-soluble powders with a water-soluble polymer, such as polyethylene glycol (PEG). In the molten state and if the drug dissolves in this carrier (PEG), a molecular dispersion of the drug in the carrier results. Upon solidification, a solid-dispersion is formed which can be pulverized and tableted or encapsulated. When this powder is placed in water, the water-soluble carrier rapidly dissolves leaving the poorly soluble drug enveloped in water, thus forming a solution.

The use of micronized drugs is not confined to oral preparations. For example, ophthalmic ointments and topical ointments utilize micronized drugs for their preferred release characteristics and nonirritating quality after application.

Due to the different rates and degrees of absorption obtainable from drugs of various particle size, products of the same drug substance prepared by two or more reliable pharmaceutical manufacturers may result in different degrees of therapeutic response in the same individual. A classic example of this occurs with phenytoin sodium capsules where there are two distinct forms. The first is the rapid-release type, i.e., Prompt Phenytoin Sodium Capsules, USP, and the second is the slow-dissolution type, i.e., Extended Phenytoin Sodium Capsules, USP. The former has a dissolution rate of not less than 85% in 30 minutes and is recommended for patient use 3 to 4 times per day. The latter has a slower dissolution rate, e.g., 15 to 35% in 30 minutes, which lends itself for use in patients who could be dosed less frequently. Because of such differences in formulation for a number of drugs and drug products, it is generally advisable for a person to continue taking the same brand of medication, provided it produces the desired therapeutic effect.

Physical Pharmacy Capsule 4.1   **Particle Size, Surface Area and Dissolution Rate**

Particle size has an effect on dissolution rate and solubility. As shown in the Noyes-Whitney equation:

$$\frac{dC}{dT} = kS(C_s - C_l)$$

where dC/dT is the rate of dissolution (concentration with respect to time),

  k is the dissolution rate constant
  S is the surface area of the particles,
  C_s is the concentration of the drug in the immediate proximity of the dissolving particle, i.e., the solubility of the drug,
  C_l is the concentration of the drug in the bulk fluid.

It is evident that the "C_s" cannot be significantly changed, the "C_l" is often under sink conditions (an amount of the drug is used that is less than 20% of its solubility) and "k" comprises many factors such as agitation, temperature. This leaves the "S," surface area, as a factor that can affect the rate of dissolution.

An increase in the surface area of a drug will, within reason, increase the dissolution rate. Circumstances when it may decrease the rate would include a decrease in the "effective surface area," i.e., a condition in which the dissolving fluid would not be able to "wet" the particles. Wetting is the first step in the dissolution process. This can be demonstrated by visualizing a 0.75 inch diameter by 1/4 inch thick tablet. The surface area of the tablet can be increased by drilling a series of 1/16 inch holes in the tablet. However, even though the surface area has been increased, the dissolution fluid, i.e., water, would not necessarily be able to penetrate into the new holes due to surface tension, etc., and displace the air. Adsorbed air and other factors can decrease the effective surface area of a dosage form, including powders. This is the reason that particle size reduction does not always result in an increase in dissolution rate. One can also visualize a powder that has been comminuted to a very fine state of subdivision and when it is placed in a beaker of water, the powder floats due to the entrapped and adsorbed air. The "effective surface area" is not the same as the actual "surface area" of the resulting powder.

Patients who are stabilized on one brand of drug should not be switched to another unless necessary. However, when a change is necessary, appropriate blood or plasma concentrations of the drug should be monitored until the patient is stabilized on the new product.

Occasionally, a rapid rate of drug absorption is not desired in a pharmaceutical preparation. Research pharmacists, in providing sustained rather than rapid action in certain preparations, may employ agents of varying particle size to provide a controlled dissolution and absorption process. Summaries of the physical chemical principles of particle size reduction and the relation of particle size to surface area, dissolution, and solubility may be found in the Physical Pharmacy Capsules in Chapters 3 and 6.

Crystal or Amorphous Drug Form

Solid drug materials may occur as pure crystalline substances of definite identifiable shape or as amorphous particles without definite structure. The amorphous or crystalline character of a drug substance may be of considerable importance to its ease of formulation and handling, its chemical stability, and, as has been recently shown, even its biological activity. Certain medicinal agents may be produced to exist in either a crystalline or an amorphous state. Since the amorphous form of a chemical is usually more soluble than the crystalline form, different extents of drug absorption may result with consequent differences in the degree of pharmacologic activity obtained from each. Experiences with two antibiotic substances, novobiocin and chloramphenicol palmitate, have revealed that these materials are essentially inactive when administered in crystalline form, but when they are administered in the amorphous form, absorption from the gastrointestinal tract proceeds rapidly with good therapeutic response. In other instances, crystalline forms of drugs may be used because of greater stability than the corresponding amorphous

forms. For example, the crystalline forms of penicillin G as either the potassium or sodium salt are considerably more stable than the analogous amorphous forms. Thus, in formulation work involving penicillin G, the crystalline forms are preferred and result in excellent therapeutic response.

The hormonal substance insulin presents another striking example of the different degree of activity that may result from the use of different physical forms of the same medicinal agent. Insulin is the active principle of the pancreas gland and is vital to the body's metabolism of glucose. The hormone is produced by two means. The first is by extraction procedures from either beef or pork pancreas. The second process involves a biosynthetic process with strains of *Escherichia coli*, i.e., recombinant DNA. Insulin is used by man as replacement therapy, by injection, when his body's production of the hormone is insufficient. Insulin is a protein, which, when combined with zinc in the presence of acetate buffer, forms an extremely insoluble zinc-insulin complex. Depending on the pH of the acetate buffer solution, the complex may be an amorphous precipitate or a crystalline material. Each type is produced commercially to take advantage of their unique absorption characteristics.

The amorphous form, referred to as *semilente insulin* or Prompt Insulin Zinc Suspension, USP, is rapidly absorbed upon intramuscular or subcutaneous (under the skin) injection. The larger crystalline material, called *ultralente insulin* or Extended Insulin Zinc Suspension, USP, is more slowly absorbed with a resultant longer duration of action. By combining the two types in various proportions, a physician is able to provide his patients with intermediate acting insulin of varying degrees of onset and duration of action. A physical mixture of 70% of the crystalline form and 30% of the amorphous form, called *lente insulin* or Insulin Zinc Suspension, USP, is commercially available and provides an intermediate acting insulin preparation that meets the requirements of many diabetics.

Some medicinal chemicals that exist in crystalline form are capable of forming different types of crystals, depending upon the conditions (temperature, solvent, time) under which crystallization is induced. This property, whereby a single chemical substance may exist in more than one crystalline form, is known as "polymorphism." Only one form of a pure drug substance is stable at a given temperature and pressure with the other forms, called metastable forms, converting in time to the stable crystalline form. It is therefore not unusual for a metastable form of a medicinal agent to change

form even when present in a completed pharmaceutical preparation, although the time required for a complete change may exceed the normal shelf-life of the product itself. However, from a pharmaceutical point of view, any change in the crystal structure of a medicinal agent may critically affect the stability and even the therapeutic efficacy of the product in which the conversion takes place.

The various polymorphic forms of the same chemical generally differ in many physical properties, including their solubility and dissolution characteristics, which are of prime importance to the rate and extent of drug absorption into the body's system. These differences are manifest so long as the drug is in the solid state. Once solution is effected, the different forms are indistinguishable one from another. Therefore, differences in drug action, pharmaceutically and therapeutically, can be expected from polymorphs contained in solid dosage forms as well as in liquid suspension. The use of metastable forms generally results in higher solubility and dissolution rates than the respective stable crystal forms of the same drug. If all other factors remain constant, more rapid and complete drug absorption will likely result from the metastable forms than from the stable form of the same drug. On the other hand, the stable polymorph is more resistant to chemical degradation and because of its lower solubility is frequently preferred in pharmaceutical suspensions of insoluble drugs. If metastable forms are employed in the preparation of suspensions, their gradual conversion to the stable form may be accompanied by an alteration in the consistency of the suspension itself, thereby affecting its permanency. In all instances, the advantages of the metastable crystalline forms in terms of increased physiologic availability of the drug must be balanced against the increased product stability when stable polymorphs are employed. Sulfur and cortisone acetate are two examples of drugs that exist in more than one crystalline form and are frequently prepared in pharmaceutical suspensions. In fact, cortisone acetate is reported to exist in at least five different crystalline forms. It is possible for the commercial products of two manufacturers to differ in stability and in the therapeutic effect, depending upon the crystalline form of the drug used in the formulation.

Salt Forms

The dissolution rate of a salt form of a drug is generally quite different from that of the parent compound. Sodium and potassium salts of weak

organic acids and hydrochloride salts of weak organic bases dissolve much more readily than do the respective free acids or bases. The result is a more rapid saturation of the diffusion layer surrounding the dissolving particle and the consequent more rapid diffusion of the drug to the absorption sites.

Numerous examples could be cited to demonstrate the increased rate of drug dissolution due to the use of the salt form of the drug rather than the free acid or base, but the following will suffice: the addition of the ethylenediamine moiety to theophylline increases the water solubility of theophylline 5-fold. The use of the ethylenediamine salt of theophylline has allowed the development of oral aqueous solutions of theophylline and diminished the need to use hydroalcoholic mixtures, e.g., elixirs.

Other Factors

The *state of hydration* of a drug molecule can affect its solubility and pattern of absorption. Usually the anhydrous form of an organic molecule is more readily soluble than the hydrated form. This characteristic was demonstrated with the drug ampicillin, when the anhydrous form was shown to have a greater rate of solubility than the trihydrate form (4). The rate of absorption for the anyhdrous form was greater than that for the trihydrate form of the drug.

Once swallowed, a drug is placed in the gastrointestinal tract where its solubility can be affected not only by the pH of the environment, but by the normal components of the tract and the foodstuffs which may be present. A drug may interact with one of the other agents present to form a chemical complex which may result in reduced drug solubility and decreased drug absorption. The classic example of this complexation phenomenon is that which occurs between tetracycline analogues and certain cations, e.g., calcium, magnesium, aluminum, resulting in a decreased absorption of the tetracycline derivative. Also, if the drug becomes *ad*sorbed onto insoluble material in the tract, its availability for absorption may be correspondingly reduced.

Bioavailability and Bioequivalence

The term *bioavailability* describes the *rate* and *extent* to which an active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action. The term *bioequivalence* refers to the *comparison* of bioavail-

abilities of different formulations, drug products, or batches of the same drug product.

The availability to the biologic system of a drug substance formulated into a pharmaceutical product is integral to the goals of dosage form design and paramount to the effectiveness of the medication. The study of a drug's bioavailability depends on the drug's absorption or entry into the systemic circulation, and studying the pharmacokinetic profile of the drug or its metabolite(s) over time in the appropriate biologic system, e.g., blood, plasma, urine. Graphically, bioavailability of a drug is portrayed by a concentration-time curve of the administered drug in an appropriate tissue system, e.g., plasma (Fig. 4.4). Bioavailability data are used to determine: 1) the amount or proportion of drug absorbed from a formulation or dosage form; 2) the rate at which the drug was absorbed; 3) the duration of the drug's presence in the biologic fluid or tissue; and, when correlated with patient response, and 4) the relationship between drug blood levels and clinical efficacy and toxicity.

During the product development stages of a proposed drug product, pharmaceutical manufacturers employ bioavailability studies to compare different formulations of the drug substance to ascertain the one which allows the most desirable absorption pattern. Later, bioavailability studies may be used to compare the availability of the drug substance from different production batches of the product. They may also be used to compare the availability of the drug substance from different dosage forms (as tablets, capsules, elixirs, etc.), or from the same dosage form produced by different (competing) manufacturers.

FDA Bioavailability Submission Requirements

The FDA requires bioavailability data submissions in the following instances (5).

1. *New Drug Applications (NDAs)*. A section of each NDA is required to describe the human pharmacokinetic data and human bioavailability data, or information supporting a waiver of the bioavailability data requirement (see waiver provisions following).
2. *Abbreviated New Drug Applications (ANDAs)*. In vivo bioavailability data are required unless information is provided and accepted supporting a waiver of this requirement (see waiver provisions following).
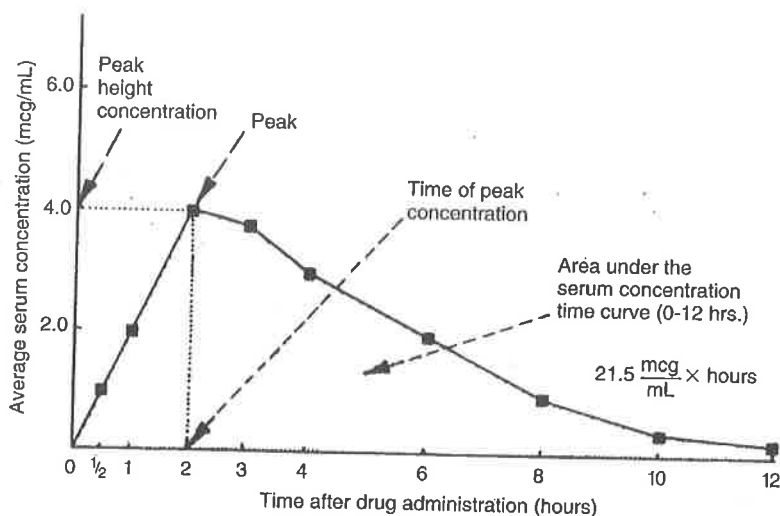
Fig. 4.4 *Serum concentration-time curve showing peak height concentration, time of peak concentration, and area under the curve. (Courtesy of D.J. Chodos and A.R. DiSanto, The Upjohn Company.)*

3. *Supplemental Applications.* In vivo bioavailability data are required if there is a change in the:
   a. Manufacturing process, product formulation or dosage strength, beyond the variations provided for in the approved NDA.
   b. Labeling, to provide for a new indication for use of the drug product and, if clinical studies are required, to support the new indication.
   c. Labeling, to provide for a new or additional dosage regimen for a special patient population (e.g., infants) if clinical studies are required to support the new or additional dosage regimen.

Conditions under which the FDA *may* waive the in-vivo bioavailability requirement include:

1. The product is a solution intended solely for intravenous administration, and contains the same active agent, in the same concentration and solvent, as a product previously approved through a full NDA.
2. The drug product is administered by inhalation as a gas or vapor, and contains the same active agent, in the same dosage form, as a product previously approved through a full NDA.
3. The drug product is an oral solution, elixir, syrup, tincture or similar other solubilized form and contains the same active agent in the same concentration as a previously approved drug product through a full NDA, and contains no inactive ingredient known to significantly affect absorption of the active drug ingredient.
4. The drug product is a topically applied preparation (e.g., ointment) intended for local therapeutic effect.
5. The drug product is an oral dosage form that is not intended to be absorbed (e.g., antacid or radiopaque medium).
6. The drug product is a solid oral dosage form that has been demonstrated to be identical, or sufficiently similar, to a drug product that has met the in-vivo bioavailability requirement.

Most of the bioavailability studies have been applied to drugs contained in solid dosage forms intended to be administered orally for systemic effects. The emphasis in this direction has been primarily due to the proliferation of competing products on the market in recent years, particularly the nonproprietary (generic) capsules and tablets, and the knowledge that certain drug entities when formulated and manufactured differently into solid dosage forms are particularly prone to variations in biologic availability. Thus, the present discussions will be centered around solid dosage forms. However, this is not to imply that systemic drug absorption is not intended from other routes of administration or other dosage forms, or that bioavailability problems may not exist from these products as well. Indeed, drug absorption from other routes is affected by the physicochemical properties of the

drug and the formulative and manufacturing aspects of the dosage form design.

Blood (or Serum or Plasma) Concentration-Time Curve

Following the oral administration of a medication, if blood samples are drawn from the patient at specific time intervals and analyzed for drug content, the resulting data may be plotted on ordinary graph paper to yield the type of drug blood level curve presented in Figure 4.4. The vertical axis of this type of plot characteristically presents the concentration of drug present in the blood (or serum or plasma) and the horizontal axis presents the time the samples were obtained following the administration of the drug. When the drug is first administered (time zero), the blood concentration of the drug should also be zero. As the drug passes into the stomach and/or intestine, it is released from the dosage form, eventually dissolves, and is absorbed. As the sampling and analysis continue, the blood samples reveal increasing concentrations of drug until the maximum (peak) concentration (C_{max}) is reached. Then, the blood level of the drug progres-

sively decreases and, if no additional dose is given, eventually falls to zero. The diminished blood level of drug after the peak height is reached indicates that the rate of drug elimination from the blood stream is greater than the rate of drug absorption into the circulatory system. Drug absorption does not terminate after the peak blood level is reached, but may continue for some time. Similarly the process of drug elimination is a continuous one. It begins as soon as the drug first appears in the blood stream and continues until all of the drug has been eliminated. When the drug leaves the blood it may be found in various body tissues and cells for which it has an affinity until ultimately it is excreted as such or as drug metabolites in the urine or via some other route (Fig. 4.5). A urinalysis for the drug or its metabolites may be used to indicate the extent of drug absorption and/or the rate of drug elimination from the body.

Parameters for Assessment and Comparison of Bioavailability

In discussing the important parameters to be considered in the comparative evaluation of the blood
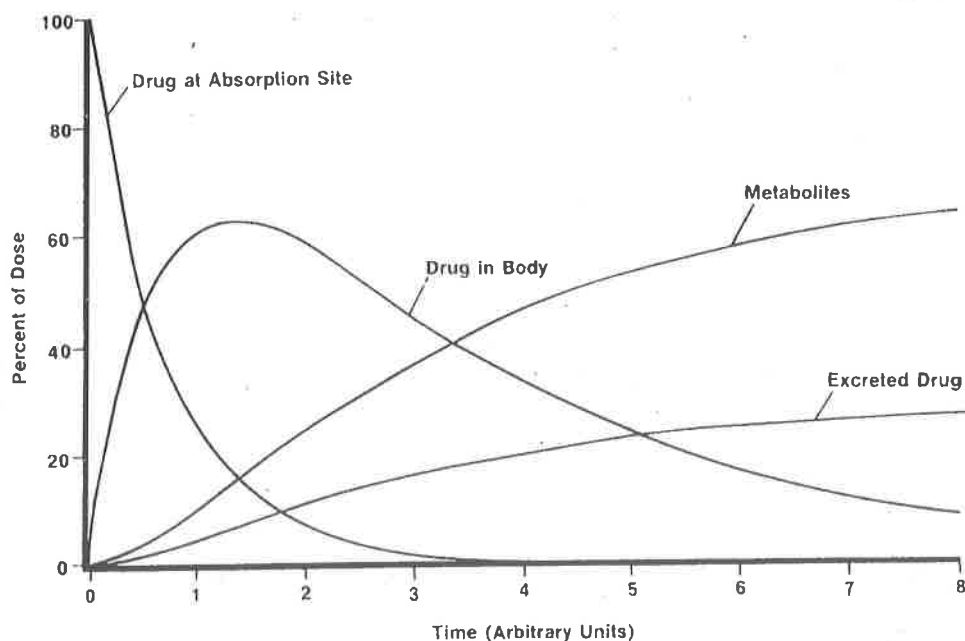

Fig. 4.5   *Time course of drug in the body. (Reprinted with permission from Rowland M, Tozer TN. Clinical Pharmacokinetics. 2nd Ed., Philadelphia: Lea & Febiger, 1989.)*

level curves following the oral administration of single doses of two formulations of the same drug entity, Chodos and DiSanto (6) list the following:

1. The Peak Height Concentration (C_{max})
2. The Time of the Peak Concentration (T_{max})
3. The Area Under the Blood (or serum or plasma) Concentration-Time Curve (AUC)

Using Figure 4.4 as an example, the height of the peak concentration is equivalent to 4.0 μg/mL of drug in the serum; the time of the peak concentration is 2 hours after administration; and the area under the curve from 0 to 12 hours is calculated as 21.5 μg/mL × hours. The meaning and use of these parameters are further explained as follows.

Peak Height

Peak height concentration is the maximum drug concentration (C_{max}) observed in the blood plasma or serum following a dose of the drug. For conventional dosage forms, as tablets and capsules, the C_{max} will usually occur at only a single time point, referred to as T_{max}. The amount of drug is usually expressed in terms of its concentration in relation to a specific volume of blood, serum, or plasma. For example, the concentration may be expressed as g/100 mL, μg/mL or mg% (mg/100 mL). Figure 4.6 depicts concentration-time curves showing different peak height concentrations for *equal* amounts of drug from two different formulations following oral administration. The horizontal line drawn across the figure indicates that the minimum effective concentration (MEC) for the drug substance is

4.0 μg/mL. This means that in order for the patient to exhibit an adequate response to the drug, this concentration in the blood must be achieved. Comparing the blood levels of drug achieved after the oral administration of equal doses of formulations "A" and "B" in Figure 4.6, formulation "A" will achieve the required blood levels of drug to produce the desired pharmacologic effect whereas the administration of formulation "B" will not. On the other hand, if the minimum effective concentration for the drug was 2.0 μg/mL and the mimimum toxic concentration (MTC) was 4.0 μg/mL as depicted in Figure 4.7, equal doses of the two formulations would result in toxic effects produced by formulation "A" but only desired effects by formulation "B." The objective in the individual dosing of a patient is to achieve the MEC but not the MTC.

The *size* of the dose administered influences the blood level concentration and C_{max} for that drug substance. Figure 4.8 depicts the influence of dose on the blood level time curve for a hypothetical drug administered by the same route and in the same dosage form. In this example, it is assumed that all doses are completely absorbed and eliminated at the same rates. As the dose increases, the C_{max} is proportionately higher and the area-under the-curve (AUC) proportionately greater. The peak time, T_{max}, is the same for each dose.

Time of Peak

The second parameter of importance in assessing the comparative bioavailability of two formulations is the time required to achieve the maximum level of drug in the blood (T_{max}). In Figure 4.6, the
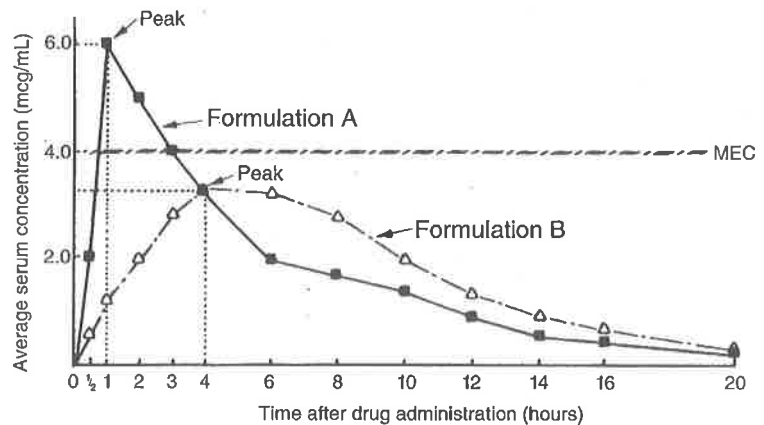

Fig. 4.6　*Serum concentration-time curve showing different peak height concentrations for equal amounts of drug from two different formulations following oral administration. (Courtesy of D.J. Chodos and A.R. DiSanto, The Upjohn Company.)*
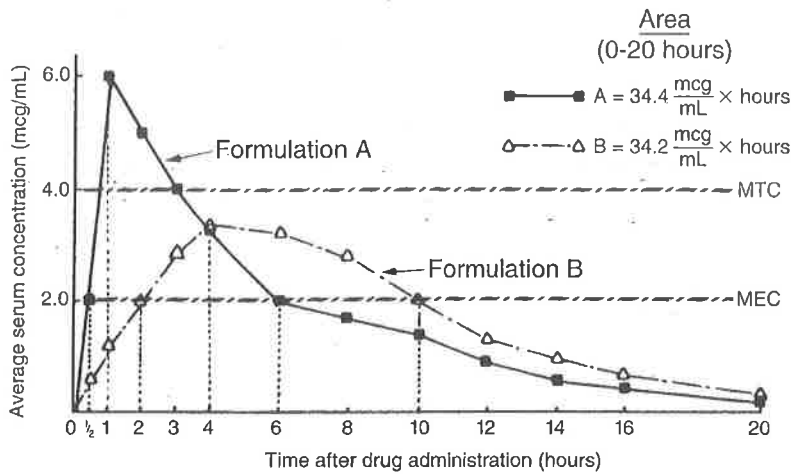
Fig. 4.7   *Serum concentration-time curve showing peak height concentrations, peak height times, times to reach minimum effective concentration (MEC) and areas under the curves for equal amounts of drug from two different formulations following oral administration. (Courtesy of D.I. Chodos and A.R. DiSanto, The Upjohn Company.)*

time required to achieve the peak serum concentration of drug is 1 hour for formulation "A" and 4 hours for formulation "B." This parameter reflects the *rate* of drug absorption from a formulation. It is the rate of drug absorption that determines the time needed for the minimum effective concentration to be reached and thus for the initiation of the desired pharmacologic effect. The rate of drug absorption also influences the period over which the drug enters the blood stream and therefore affects the duration of time that the drug is maintained in the blood. Looking at Figure 4.7, formulation "A" allows the drug to reach the MEC within 30 minutes following administration and a peak concentration in 1 hour. Formulation "B" has a slower rate of drug release. Drug from this formulation reached the MEC 2 hours after administration and its peak concentration 4 hours after administration. Thus formulation "A" permits the greater rate of drug absorption; it allows drug to reach both the MEC and its peak height sooner than drug formulation "B." On the other hand, formulation "B" provides the greater duration of time for drug concentrations maintained above the MEC, 8 hours (from 2 to 10 hours following administration) to 5 1/2 hours (from 30 minutes to 6 hours following administration) for formulation "A." Thus, if a rapid onset of action is desired, a formulation similar to "A" would be preferred, but, if a longer duration of action is desired rather than a rapid onset of action, a formulation similar to "B" would be preferred.
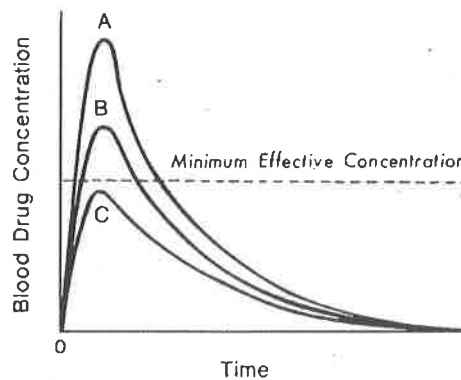

Fig. 4.8   *The influence of dose size on the resultant blood drug concentration-time curves when three different doses of the same drug are administered and the rates of drug absorption and elimination are equal after the three doses. A = 100 mg, B = 80 mg, C = 50 mg. (Reprinted with permission from Ueda CT. Concepts in Clinical Pharmacology. Essentials of Bioavailability and Bioequivalence. The Upjohn Company, 1979).*

In sum, changes in the *rate* of drug absorption will result in changes in the values of both C_{max} and T_{max}. Each product has its own characteristic rate of absorption. When the *rate* of absorption is decreased, the C_{max} is lowered and T_{max} occurs at a later time. If the doses of the drugs are the same and presumed completely absorbed, as in Figure 4.7, the AUC for each is essentially the same.

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Area Under the Serum Concentration Time Curve

The area under the curve (AUC) of a concentration-time plot (see Fig. 4.4) is considered representative of the total amount of drug absorbed into the circulation following the administration of a single dose of that drug. Equivalent doses of a drug, when fully absorbed, would produce the same AUC. Thus, two curves dissimilar in terms of peak height and time of peak, as those in Figure 4.7, may be similar in terms of area under the curve, and thus in the amount of drug absorbed. As indicated in Figure 4.7, the area under the curve for formulation "A" is 34.4 µg/mL × hours and for formulation "B" is 34.2 µg/mL × hours, essentially the same. If equivalent doses of drug in different formulation produce *different* AUC values, differences exist in the *extent* of absorption between the formulations. Figure 4.9 depicts concentration-time curves for three different formulations of equal amounts of drug with greatly different areas under the curve. In this example, formulation "A" delivers a much greater amount of drug to the circulatory system than do the other two formulations. In general, the smaller the AUC, the less drug absorbed.

The area under the curve may be measured mathematically, using a technique known as the trapezoidal rule, and is reported in amount of drug/volume of fluid × time (e.g., µg/mL × hours; g/100 × hours; etc.).

According to the trapezoidal rule, the area beneath a drug concentration-time curve can be estimated through the assumption that the AUC can be represented by a series of trapezoids (quadrilateral planes having two parallel and two nonparallel sides). The total AUC would be the sum of the areas of the individual trapezoids. The area of each trapezoid is calculated taking $1/2(C_{n+1} + C_n)(t_n - t_{n-1})$, where C_n and t_n are drug concentrations in the blood plasma, or serum, and time, respectively. The use of the trapezoid is demonstrated by the data reproduced in Table 4.3 and plotted into a plasma drug concentration-time curve as shown in Figure 4.10.

The fraction (F) (or bioavailability) of an orally administered drug may be calculated by comparison of the AUC after oral administration with that obtained after intravenous administration:

$$F = (AUC)_{oral}/(AUC)_{intravenous}$$

In practice, it would be rare for a drug to be completely absorbed into the circulation following oral administration. As noted earlier, many drugs undergo the first-pass effect resulting in some degree of metabolic degradation before entering the general circulation. In addition, factors of drug product formulation, drug dissolution, chemical and physical interactions with the gastrointestinal contents, gastric emptying time, intestinal motility, and others contribute to the incomplete absorption of an administered dose of a drug. The oral dosage strengths of many commerical products are based on considerations of the proportion of the dose administered that is expected to be absorbed and available to its site of action in order to produce the
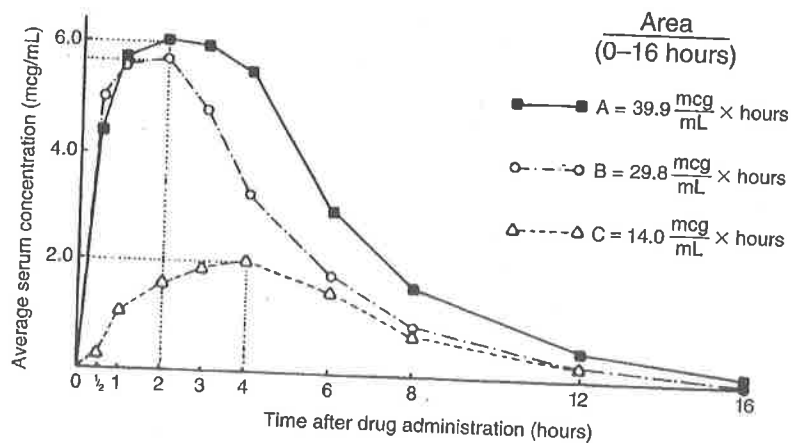

Fig. 4.9   *Serum concentration-time curve showing peak height concentrations, peak height times, and areas under the curves for equal amounts of drugs from three different formulations following oral administration. (Courtesy of Chodos DJ, DiSanto AR, The Upjohn Company.)*

Table 4.3. Determination of AUC Using the Trapezoidal Rule for the Following Plasma Drug Concentration-Time Data*

Sample (n)	Time (hr)	Plasma Concentration (μg/mL)	$AUC/t_n t_{n-1}$ (μg/mL × hr)
1	0	0	½ (0 + 1)(0.5 − 0) = 0.25
2	0.5	1	½ (1 + 11)(1 − 0.5) = 3.00
3	1.0	11	½ (11 + 28)(1.5 − 1) = 9.75
4	1.5	28	½ (28 + 30)(2 − 1.5) = 14.50
5	2	30	½ (30 + 21)(3 − 2) = 25.50
6	3	21	½ (21 + 17)(4 − 3) = 19.00
7	4	17	½ (17 + 9)(6 − 4) = 26.00
8	6	9	½ (9 + 4)(8 − 6) = 13.00
9	8	4	½ (4 + 2)(10 − 8) = 6.00
10	10	2	½ (2 + 1)(12 − 10) = 3.00
11	12	1	½ (1 + 0)(18 − 12) = 3.00
12	18	0	AUC = 123.00

*Reprinted with permission from Ueda CT. Concepts in Clinical Pharmacology. Essentials of Bioavailability and Bioequivalence. The Upjohn Company, 1979.

desired drug blood level and/or therapeutic response. The absolute bioavailability following oral dosing is generally compared to intravenous dosing. As examples, the mean oral absorption of a dose of verapamil (Calan) is reported to be 90%; enalapril (Vasotec) 60%; diltiazem (Cardizem) about 40%, and lisinopril (Zestril) about 25%. However, there is large intersubject variability, and the absorbed doses may vary patient-to-patient.

Bioequivalence of Drug Products

A great deal of discussion and scientific investigation has been devoted recently to the problem of determining the equivalence between drug products of competing manufacturers.

The rate and extent to which a drug in a dosage form becomes available for biologic absorption or utilization depends in great measure upon the materials utilized in the formulation and also on the method of manufacture. Thus, the same drug when formulated in *different* dosage forms may be found to possess different bioavailability characteristics and hence exhibit different clinical effectiveness. Further, two seemingly "identical" or "equivalent" products, of the same drug, in the same dosage strength and in the *same* dosage form type, but differing in formulative materials or method of manufacture, may vary widely in bioavailability and thus in clinical effectiveness.

Dissolution requirements for capsules and tablets are included in the USP and are integral to bioavailability. Experience has shown that where bioinequivalence has been found between two supposedly equivalent products, dissolution testing can help to define the product differences. According to the USP, significant bioavailability and bioinequivalence problems may be revealed through dissolution testing and are generally the result of one or more of the following causal factors: the drug's particle size; excessive amounts of the lubricant magnesium stearate in the formulation; coating materials, especially shellac; and inadequate amounts of tablet or capsule disintegrants.

The following terms are used by the Food and Drug Administration to define the type or level of "equivalency" between drug products (5).

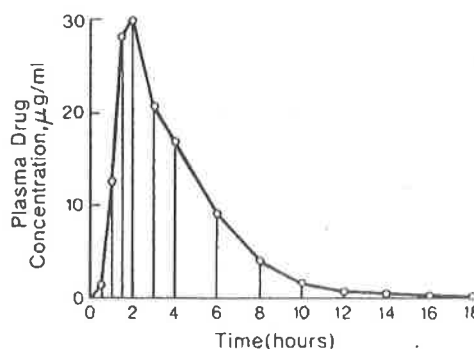*Pharmaceutical equivalents* are drug products that contain identical amounts of the identical active

Fig. 4.10 *Estimation of area under the drug concentration-time curve using the trapezoidal rule (see Table 4.3 for raw data). (Reprinted with permission from Ueda CT. Concepts in Clinical Pharmacology. Essentials of Bioavailability and Bioequivalence. The Upjohn Company, 1979).*

drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, in identical dosage forms, but not necessarily containing the same inactive ingredients, and that meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

Bioequivalent drug products are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption, and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, or are considered medically insignificant for the particular drug product studied.

In addition, the term *therapeutic equivalents* has been used to indicate pharmaceutical equivalents which, when administered to the same individuals in the same dosage regimens, will provide essentially the same therapeutic effect.

Differences in bioavailability have been demonstrated for a number of products involving the following and other drugs: tetracycline, chloramphenicol, digoxin, phenylbutazone, warfarin, diazepam, levodopa, and oxytetracycline. Not only has bio-*in*equivalence been shown to exist in products of different manufacturers but there have also been variations in the bioavailability of different batches of drug products from the same manufacturer. Variations in the bioavailability of certain drug products have resulted in some therapeutic failures in patients who have taken two inequivalent drug products in the course of their therapy.

The most common experimental plan to compare the bioavailability of two drug products is the simple *crossover design study.* In this method, each of the 12 to 24 individuals in the group of carefully matched subjects (usually healthy adult males between 18 and 40 years of age of similar height and weight) is administered both products under fasting conditions and essentially serves as his own control. To avoid bias of the test results, each test subject is randomly assigned one of the two products for the first phase of the study. Once the first assigned product is administered, samples of blood or plasma are drawn from the subjects at predetermined times and analyzed for the active drug moiety and its metabolites as a function of time. The same procedure is then repeated (*crossover*) with the second product after an appropriate interval of time, i.e., a washout period to ensure that there is no residual amount of drug from the first administered product that would artificially inflate the test results of the second administered product. Afterward, the patient population data are tabulated and the parameters used to assess and compare bioavailability, i.e., C_{max}, T_{max}, AUC, are then analyzed with statistical procedures. Statistical differences in bioavailability parameters may not always be clinically significant in therapeutic outcome.

Inherent differences in individuals result in different patterns of drug absorption, metabolism and excretion. These differences must be statistically analyzed to separate them from the factors of bioavailability related to the products themselves. The value in the crossover-designed experiment is that each individual serves as his own control by taking each of the products. Thus, inherent differences as mentioned between individuals is minimized.

Absolute bioequivalency between drug products rarely, if ever, occurs. Such absolute equivalency would yield serum concentration-time curves for the products involved that would be exactly superimposable. This simply is not expected of products which are made at different times, in different batches, or indeed by different manufacturers. However, some expectations of bioequivalency are expected of products which are considered to be of equivalent merit for therapy.

In most studies of bioavailability, the originally marketed product (frequently referred to as the "prototype,'"'pioneer,"or"innovator"drug product) is recognized as the established product of the drug and is utilized as the standard for the bioavailability comparative studies.

As a result of the implementation of the Drug Price Competition and Patent Term Restoration Act of 1984, many additional drugs became available in generic form. Prior to the 1984 act, only those drugs

marketed before 1962 could be processed by an Abbreviated New Drug Application (ANDA). The ANDA process does not require the sponsor to repeat costly clinical research on active ingredients already found to be safe and effective. The 1984 Act extended the eligibility for ANDA processing to drugs first marketed after 1962, making generic versions immediately possible for many additional off-patent drugs previously available only as brand name (pioneer) products.

According to the FDA, a generic drug is considered bioequivalent if the rate and extent of absorption do not show a significant difference from that of the pioneer drug when administered at the same molar dose of the therapeutic ingredient under the same experimental conditions (7). Because, in the case of a systemically absorbed drug, blood levels even if from an identical product may vary in different subjects, in bioequivalence studies each subject receives both the pioneer and the test drug and thus serves as his own control.

Under the 1984 act, to gain FDA approval a generic drug product must:

- Contain the same active ingredients as the pioneer drug (inert ingredients may vary)
- Be identical in strength, dosage form, and route of administration
- Have the same indications and precautions for use and other labeling instructions
- Be bioequivalent
- Meet the same batch-to-batch requirements for identity, strength, purity, and quality
- Be manufactured under the same strict standards of FDA's Current Good Manufacturing Practice regulations as required for pioneer products

In the design and evaluation of bioequivalence, the FDA employs the "80/20 rule." This rule requires that a study be large enough to provide an 80% probability to detect a 20% difference in average bioavailability. The allowance of a statistical variability of ±20% in bioequivalence applies to both reformulated pioneer drugs and generics. If a pioneer manufacturer reformulates an FDA-approved product, the subsequent formulation must meet the same bioequivalency standards that are required of generic manufacturers of that product (i.e., the approved bioavailability standard for that product).

The FDA recommends generic substitution only among products that it has evaluated to be therapeutically equivalent. Since 1980, the Agency has prepared an annual *Approved Drug Products with*

Therapeutic Equivalence Evaluations (known as the "Orange Book") which is published in the USP-DI, Volume III"Approved Drug Products and Legal Requirements." This publication is regularly updated and contains information on about 10,000 approved prescription drug products. About 7,500 of these are available from more than a single manufacturer, with only about 10% considered therapeutically *in*equivalent to the pioneer products. For example, the FDA rates all conjugated estrogens and esterified estrogen products as"not therapeutically equivalent," because no manufacturer to date has submitted an acceptable in vivo bioequivalence study. Therefore, the FDA does not recommend that these products be substituted for each other.

The variables that can contribute to the differences between products are many (Table 4.4). For instance in the manufacture of a tablet, different

Table 4.4.   Some Factors Which Can Influence the Bioavailability of Orally Administered Drugs

Drug Substance Physiochemical Properties
　Particle Size
　Crystalline or Amorphous Form
　Salt Form
　Hydration
　Lipid/Water Solubility
　pH and pK_a
Pharmaceutic Ingredients and Dosage Form Characteristics
　Pharmaceutic Ingredients
　　Fillers
　　Binders
　　Coatings
　　Disintegrating Agents
　　Lubricants
　　Suspending Agents
　　Surface Active Agents
　　Flavoring Agents
　　Coloring Agents
　　Preservative Agents
　　Stabilizing Agents
　Disintegration Rate (Tablets)
　Dissolution Time of Drug in Dosage Form
　Product Age and Storage Conditions
Physiologic Factors and Patient Characteristics
　Gastric Emptying Time
　Intestinal Transit Time
　Gastrointestinal Abnormality or Pathologic Condition
　Gastric Contents
　　Other drugs
　　Food
　　Fluids
　Gastrointestinal pH
　Drug Metabolism (Gut and during first passage
　　through liver).

materials or amounts of such formulative components as fillers, disintegrating agents, binders, lubricants, colorants, flavorants and coatings may be used. The particle size or crystalline form of a therapeutic or pharmaceutic component may vary between formulations. The tablet may vary in shape, size, and hardness depending upon the punches and dies selected for use by the manufacturer and the compression forces utilized in the process. During packaging, shipping and storage the integrity of the tablets may be altered by physical impact, or changes in conditions of humidity, temperature, or through interactions with the components of the container. Each of the factors noted may have an effect on the rates of tablet disintegration, drug dissolution, and consequently on the rate and extent of drug absorption. Although the bioequivalency problems are perhaps greater among tablets than for other dosage forms because of the multiplicity of variables, the same types of problems exist for the other dosage forms and must be considered in bioequivalency evaluations.

There are situations in which even therapeutically equivalent drugs may not be equally suitable for a particular patient. For example, a patient may be hypersensitive to an inert ingredient in one product (brand name or generic) that another product does not contain. Or a patient may become confused or upset if dispensed an alternate product that differs in color, flavor, shape, or packaging from that to which he or she has become accustomed. Switching between products can generate concern, and thus pharmacists need to be prudent in both initial product selection and in product interchange.

Routes of Drug Administration

Drugs may be administered by a variety of dosage forms and routes of administration, as presented in Tables 4.5 and 4.6. One of the fundamental considerations in dosage form design is whether the drug is intended for local or systemic effects. *Local* effects are achieved from direct application of the drug to the desired site of action, such as the eye, nose, or skin. *Systemic* effects result from the entrance of the drug into the circulatory system and its subsequent transport to the cellular site of its action. For systemic effects, a drug may be placed directly into the blood stream via intravenous injection or absorbed into the venous circulation following oral, or other routes of administration.

An individual drug substance may be formulated into multiple dosage forms which result in different drug absorption rates and times of onset, peak, and duration of action. This is demonstrated by Figure

Table 4.5.   Routes of Drug Administration

Term	Site
Oral	Mouth
Peroral (per os*)	Gastrointestinal tract via mouth
Sublingual	Under the tongue
Parenteral	Other than the gastrointestinal tract (by injection)
Intravenous	Vein
Intraarterial	Artery
Intracardiac	Heart
Intraspinal or intrathecal	Spine
Intraosseous	Bone
Intraarticular	Joint
Intrasynovial	Joint-fluid area
Intracutaneous or intradermal	Skin
Subcutaneous	Beneath the skin
Intramuscular	Muscle
Epicutaneous (topical)	Skin surface
Transdermal	Skin surface
Conjunctival	Conjunctiva
Intraocular	Eye
Intranasal	Nose
Aural	Ear
Intrarespiratory	Lung
Rectal	Rectum
Vaginal	Vagina

*The abbreviation "po" is commonly used on prescriptions to indicate to be swallowed.

4.11 and Table 4.7, for the drug nitroglycerin in various dosage forms. The sublingual, intravenous, and buccal forms present extremely rapid onsets of action whereas the oral (swallowed), topical ointment and topical disc present slower onsets of action but greater durations of action. The disc provides the longest duration of action, up to 24 hours following application of a single patch to the skin. The transdermal nitroglycerin disc allows a single daily dose, whereas the other forms require multiple dosing to maintain drug levels within the therapeutic window.

The difference in drug absorption between dosage forms is a function of the formulation and the route of administration. For example, a problem associated with the oral administration of a drug is that once absorbed through the lumen of the gastrointestinal tract into the portal vein, the drug may pass directly to the liver and undergo the *first-pass effect.* In essence a portion or all of the drug may be metabolized by the liver. Consequently, as the drug is extracted by the liver, its bioavailability to the body

Table 4.6. Dosage Form/Drug Delivery System Application Route of Administration Primary Dosage Forms

Oral	Tablets
	Capsules
	Solutions
	Syrups
	Elixirs
	Suspensions
	Magmas
	Gels
	Powders
Sublingual	Tablets
	Troches or lozenges
Parenteral	Solutions
	Suspensions
Epicutaneous/	Ointments
transdermal	Creams
	Infusion pumps
	Pastes
	Plasters
	Powders
	Aerosols
	Lotions
	Transdermal patches, discs, solutions
Conjunctival	Contact lens inserts
	Ointments
Intraocular/	Solutions
intraaural	Suspensions
Intranasal	Solutions
	Sprays
	Inhalants
	Ointments
Intrarespiratory	Aerosols
Rectal	Solutions
	Ointments
	Suppositories
Vaginal	Solutions
	Ointments
	Emulsion foams
	Gels
	Tablets
	Inserts, suppositories, sponge
Urethral	Solutions
	Suppositories

The bioavailability is lowest, then, for those drugs that undergo a significant first-pass effect. For these drugs, a hepatic extraction ratio, or the fraction of drug metabolized, E, is calculated. The fraction of drug that enters the system circulation and is ultimately available to exert its effect then is equal to the quantity $(1-E)$. Table 4.8 lists some drugs according to their pharmacologic class that undergo a significant first-pass effect when administered by the oral route.

To compensate for this marked effect, the drug manufacturer may consider other routes of drug administration, e.g., intravenous, intramuscular, sublingual, that avoid the first-pass effect. With these routes there will be a corresponding decrease in the dosage required when compared with oral administration.

Another consideration centers around the metabolites themselves, and whether they are pharmacologically active or inactive. If they are inactive, a larger oral dose will be required to attain the desired therapeutic effect when compared to a lower dosage in a nonfirst-pass effect route. The classic example of drug that exhibits this effect is propranolol. If, on the other hand, the metabolites are the active species, the oral dosage must be carefully tailored to the desired therapeutic effect. First-pass metabolism in this case will result in a quicker therapeutic response than that achieved by a non-first-pass effect route.
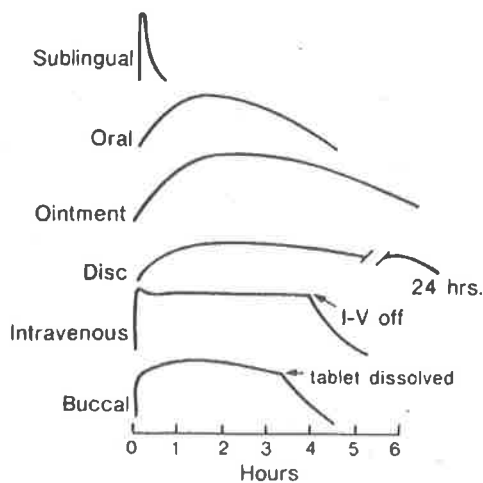

Fig. 4.11   *Blood-level curves of nitroglycerin following administration of dosage forms by various routes. (Reprinted with permission from Abrams J. Nitroglycerin and Long-Acting Nitrates in Clinical Practice. The American Journal of Medicine, Proceedings of a Symposium: First North American Conference on Nitroglycerin Therapy, June 27, 1983).*

is decreased. Thus, the bioavailable fraction is determined by the fraction of drug that is absorbed from the gastrointestinal tract and the fraction that escapes metabolism during its first pass through the liver. The bioavailable fraction (f) is the product of these two fractions as follows:

$$f = \text{Fraction of drug absorbed} \times \text{Fraction escaping first-pass metabolism}$$

Table 4.7.   Dosage and Kinetics of Nitroglycerin in Various Dosage Forms

Nitroglycerin, Dosage Form	Usual Dose (mg)	Onset of Action (Minutes)	Peak Action (Minutes)	Duration (Mins/Hours)
Sublingual	0.3–0.8	2–5	4–8	10–30 minutes
Buccal	1–3	2–5	4–10	30–300 minutes[Δ]
Oral	6.5–19.5	20–45	45–120	2–6 hours[Ω]
Ointment (2%)	½–2 inches	15–60	30–120	3–8 hours
Discs	5–10	30–60	60–180	Up to 24 hours

[Δ] Effect persists so long as tablet is intact.

[Ω] Some short-term dosing studies have demonstrated effects to 8 hours.

Reprinted with permission from Abrams J. Nitroglycerin and Long-Acting Nitrates in Clinical Practice. Am J Med. Proceedings of a Symposium: First North American Conference of Nitroglycerin Therapy, June 27, 1983, p. 88.

One must remember also that the flow of blood through the liver can be decreased under certain conditions. Consequently, the bioavailability of those drugs that undergo a first-pass effect then would be expected to increase. For example, during cirrhosis the blood flow to the kidney is dramatically decreased and efficient hepatic extraction by enzymes responsible for a drug's metabolism also falls off. Consequently, in cirrhotic patients the dosage of drug that undergoes a first-pass effect from oral administration will have to be reduced to avoid toxicity.

Oral Route

Drugs are most frequently taken by oral administration. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken orally are swallowed. Of these, most are taken for the *systemic* drug effects that result after absorption from the various surfaces along the gastrointestinal tract. A few drugs, such as antacids, are swallowed for their local action within the confines of the gastrointestinal tract.

Compared with alternate routes, the oral route is considered the most natural, uncomplicated, convenient, and safe means of administering drugs. Disadvantages of the oral route include slow drug response (when compared with parenterally administered drugs); chance of irregular absorption of drugs, depending upon such factors as constitutional make-up, the amount or type of food present within the gastrointestinal tract; and the destruction of certain drugs by the acid reaction of the stomach or by gastrointestinal enzymes.

Dosage Forms Applicable

Drugs are administered by the oral route in a variety of pharmaceutical forms. The most popular

are tablets, capsules, suspensions, and various pharmaceutical solutions. Briefly, *tablets* are solid dosage forms prepared by compression or molding and contain medicinal substances with or without suitable diluents, disintegrants, coatings, colorants, and other pharmaceutical adjuncts. Diluents are fillers used in preparing tablets of the proper size and consistency. Disintegrants are used for the break-up or separation of the tablet's compressed ingredients. This ensures prompt exposure of drug particles to the dissolution process thereby enhancing drug absorption, as shown in Figure 4.12. Tablet coatings are of several types and for several different purposes. Some called *enteric coatings* are employed to permit safe passage of a tablet through the acid environment of the stomach where certain drugs may be destroyed, to the more suitable juices of the intestines where tablet dissolution safely takes place. Other coatings protect the drug substance from the destructive influences of mois-

Table 4.8.   Examples of Drugs that Undergo Significant Liver Metabolism and Exhibit Low Bioavailability when Administered by First-pass Routes

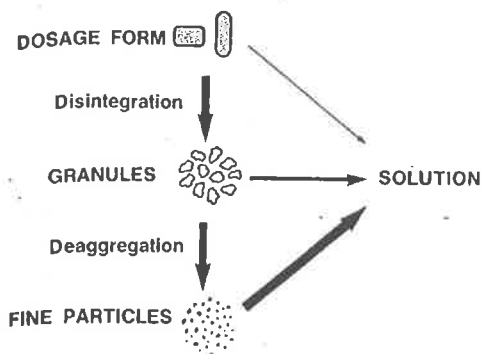| Drug Class	Examples
Analgesics	Aspirin, meperidine, pentazocine, propoxyphene
Antianginal	Nitroglycerin
Antiarrhythmics	Lidocaine
Beta-adrenergic blockers	Labetolol, metoprolol, propranolol
Calcium channel blockers	Verapamil
Sympathomimetic amines	Isoproterenol
Tricyclic antidepressants	Desipramine, imipramine, nortriptyline

Fig. 4.12 *Schematic drawing showing disintegration of a tablet dosage form and direct availability of the contents in a capsule dosage form for dissolution and drug absorption after oral administration. (Reprinted with permission from Rowland M, Rozer TN. Clinical Pharmacokinetics. 2nd Ed. Philadelphia: Lea & Febiger, 1989).*

ture, light, and air throughout their period of storage or to conceal a bad or bitter taste from the taste buds of a patient. Commercial tablets, because of their distinctive shapes, colors, and frequently employed monograms of company symbols and code numbers facilitate identification by persons trained in their use and serve as an added protection to public health.

Capsules are solid dosage forms in which the drug substance and appropriate pharmaceutical adjuncts as fillers are enclosed in either a hard or a soft "shell," generally composed of a form of gelatin. Capsules vary in size, depending on the amount of drug to be administered, and are of distinctive shapes and colors when produced commercially. Drug materials are released from capsules faster than from tablets. Capsules of gelatin, a protein, are rapidly disfigured within the gastrointestinal tract, permitting the gastric juices to permeate and reach the contents. Because unsealed capsules have been subject to tampering by unscrupulous individuals, many capsules nowadays are sealed by fusion of the two capsule shells. Also, capsule-shaped and coated tablets, called "caplets," are increasingly utilized. These are easily swallowed but their contents are sealed and protected from tampering like tablets.

Suspensions are preparations of finely divided drugs held in suspension throughout a suitable vehicle. Suspensions taken orally generally employ an aqueous vehicle, whereas those employed for other purposes may utilize a different vehicle. Sus-

pensions of certain drugs to be used for intramuscular injection, for instance, may be maintained in a suitable oil. To be suspended, the drug particles must be insoluble in the vehicle in which they are placed. Nearly all suspensions must be shaken before use because they tend to settle. This ensures not only uniformity of the preparation but more importantly the administration of the proper dosage. Suspensions are a useful means to administer large amounts of solid drugs that would be inconveniently taken in tablet or capsule form. In addition, suspensions have the advantage over solid dosage forms in that they are presented to the body in fine particle size, ready for the dissolution process immediately upon administration. However, not all oral suspensions are intended to be dissolved and absorbed by the body. For instance, kaolin mixture with pectin, an antidiarrheal preparation, contains suspended kaolin, which acts in the intestinal tract by adsorbing excessive intestinal fluid on the large surface area of its particles.

Drugs administered in aqueous *solution* are absorbed much more rapidly than those administered in solid form, because the processes of disintegration and dissolution are not required. Pharmaceutical solutions may differ in the type of solvent employed and therefore in their fluidity characteristics. Among the solutions frequently administered orally are *elixirs*, which are solutions in a sweetened hydroalcoholic vehicle and are more mobile than water; *syrups*, which generally utilize sucrose solutions as the sweet vehicle resulting in a viscous preparation; and *solutions* themselves, which officially are preparations in which the drug substance is dissolved predominantly in an aqueous vehicle and do not for reasons of their method of preparation (e.g., injections, which must be sterilized) fall into another category of pharmaceutical preparations.

Absorption

Absorption of drugs after oral administration may occur at the various body sites between the mouth and rectum. In general, the higher up a drug is absorbed along the length of the alimentary tract, the more rapid will be its action, a desirable feature in most instances. Because of the differences in the chemical and physical nature among drug substances, a given drug may be better absorbed from the environment of one site than from another within the alimentary tract.

The oral cavity is used on certain occasions as the absorption site of certain drugs. Physically, the oral absorption of drugs is managed by allowing the drug substance to be dissolved within the oral cav-

ity with infrequent or no swallowing until the taste of the drug has dissipated. This process is accommodated by providing the drug as extremely soluble and rapidly dissolving uncoated tablets. Drugs capable of being absorbed in the mouth present themselves to the absorbing surface in a much more concentrated form than when swallowed, since drugs become progressively more diluted with gastrointestinal secretions and contents as they pass along the alimentary tract.

Currently the oral or *sublingual* (beneath the tongue) administration of drugs is regularly used for only a few drugs, with nitroglycerin and certain steroid sex hormones being the best examples. Nitroglycerin, a coronary vasodilator used in the prophylaxis and treatment of angina pectoris, is available in the form of tiny tablets which are allowed to dissolve under the tongue, producing therapeutic effects in a few minutes after administration. The dose of nitroglycerin is so small (usually 400 μg) that if it were swallowed the resulting dilute gastrointestinal concentration may not result in reliable and sufficient drug absorption. Even more important, however, is the fact that nitroglycerin is rapidly destroyed by the liver through the *first-pass effect*. Many sex hormones have been shown to be absorbed materially better from sublingual administration than when swallowed. Although the sublingual route is probably an effective absorption route for many other drugs, it has not been extensively used, primarily because other routes have proven satisfactory and more convenient for the patient. Retaining drug substances in the mouth is unattractive because of the bitter taste of most drugs.

Drugs may be altered within the gastrointestinal tract to render them less available for absorption. This may result from the drug's interaction with or binding to some normal constituent of the gastrointestinal tract or a foodstuff or even another drug. For instance, the absorption of the tetracycline group of antibiotics is greatly interfered with by the simultaneous presence of calcium. Because of this, tetracycline drugs must not be taken with milk or other calcium containing foods or drugs.

In some instances it is the intent of the pharmacist to prepare a formulation that releases the drug slowly over an extended period of time. There are many methods by which slow release is accomplished, including the complexation of the drug with another material, the combination of which is only slowly released from the dosage form. An example of this is the slow-release waxy matrix potassium chloride tablets. These are designed to release their contents gradually as they are shunted through the gastrointestinal tract. Because their contents are leached out gradually there is less incidence of gastric irritation. The intermingling of food and drug generally results in delayed drug absorption. Since most drugs are absorbed more effectively from the intestines than from the stomach, when rapid absorption is intended, it is generally desirable to have the drug pass from the stomach into the intestines as rapidly as possible. Therefore, gastric emptying time is an important factor in effecting drug action dependent upon intestinal absorption. Gastric emptying time may be increased by a number of factors, including the presence of fatty foods (more effect than proteins, which in turn have more effect than carbohydrates), lying on the back when bedridden (lying on the right side facilitates passage in many instances), and the presence of drugs (for example, morphine) that have a quieting effect on the movements of the gastrointestinal tract. If a drug is administered in the form of a solution, it may be expected to pass into the intestines more rapidly than drugs administered in solid form. As a rule, large volumes of water taken with medication facilitate gastric emptying and passage into the intestines.

The pH of the gastrointestinal tract increases progressively along its length from a pH of about 1 in the stomach to approximately pH 8 at the far end of the intestines. pH has a definite bearing on the degree of ionization of most drugs, and this in turn affects lipid solubility, membrane permeability and absorption. Because most drugs are absorbed by passive diffusion through the lipoid barrier, the lipid/water partition coefficient and the pK_a of the drugs are of prime importance to both their degree and site of absorption within the gastrointestinal tract. As a general rule, weak acids are largely *un*ionized in the stomach and are absorbed fairly well from this site, whereas weak bases are highly ionized in the stomach and are not significantly absorbed from the gastric surface. Alkalinization of the gastric environment by artificial means (simultaneous administration of alkaline or antacid drugs) would be expected to decrease the gastric absorption of weak acids and to increase that of weak bases. Strong acids and bases are generally poorly absorbed due to their high degrees of ionization.

The small intestine serves as the major absorption pathway for drugs because of its suitable pH and the great surface area available for drug absorption within its approximate 20-foot length extending from the pylorus at the base of the stomach to the junction with the large intestine at the cecum. The pH of the lumen of the intestine is

about 6.5 (see Fig. 4.3) and both weakly acidic and weakly basic drugs are well absorbed from the intestinal surface, which behaves in the ionization and distribution of drugs between it and the plasma on the other side of the membrane as though its pH were about 5.3.

Rectal Route

Some drugs are administered rectally for their local effects and others for their systemic effects. Drugs given rectally may be administered as solutions, suppositories, or ointments. *Suppositories* are defined as solid bodies of various weights and shapes intended for introduction into a body orifice (usually rectal, vaginal, or urethral) where they soften, melt, or dissolve, release their medication, and exert their drug effects. These effects simply may be the promotion of laxation (as with glycerin suppositories), the soothing of inflamed tissues (as with various commercial suppositories used to relieve the discomfort of hemorrhoids), or the promotion of systemic effects (as antinausea or antimotion sickness). The composition of the suppository base, or carrier of the medication, can greatly influence the degree and rate of drug release and should be selected on an individual basis for each drug. The use of rectal ointments is generally limited to the treatment of local conditions. Rectal solutions are usually employed as enemas or cleansing solutions.

The rectum and the colon can absorb many soluble drugs. Rectal administration for systemic action may be preferred for those drugs destroyed or inactivated by the environments of the stomach and intestines. The administration of drugs by the rectal route may also be indicated when the oral route is precluded because of vomiting or when the patient is unconscious or incapable of swallowing drugs safely without choking. Approximately 50% of a dose of drug absorbed from rectal administration is likely to bypass the liver, an important factor when considering those orally administered drugs that are rapidly destroyed in the liver by the first-pass effect. On the negative side, compared with oral administration, rectal administration of drugs is inconvenient, and the absorption of drugs from the rectum is frequently irregular and difficult to predict.

Parenteral Route

The term *parenteral* is derived from the Greek words *para,* meaning beside, and *enteron,* meaning intestine, which together indicate something done outside of the intestine and not by way of the alimentary tract. A drug administered parenterally is one injected through the hollow of a fine needle into the body at various sites and to various depths. The three primary routes of parenteral administration are subcutaneous, intramuscular (IM), and intravenous (IV) although there are others such as intracardiac and intraspinal.

Drugs destroyed or inactivated in the gastrointestinal tract or too poorly absorbed to provide satisfactory response may be parenterally administered. The parenteral route is also preferred when rapid absorption is essential, as in emergency situations. Absorption by the parenteral route is not only faster than after oral administration, but the blood levels of drug that result are far more predictable, because little is lost after subcutaneous or intramuscular injection, and virtually none by intravenous injection; this also generally permits the administration of smaller doses. The parenteral route of administration is especially useful in treating patients who are uncooperative, unconscious, or otherwise unable to accept oral medication.

One disadvantage of parenteral administration is that once the drug is injected, there is no retreat. That is, once the substance is within the tissues or is placed directly into the blood stream, removal of the drug warranted by an untoward or toxic effect or an inadvertent overdose is most difficult. By other means of administration, there is more time between drug administration and drug absorption, which becomes a safety factor by allowing for the extraction of unabsorbed drug (as by the induction of vomiting after an orally administered drug). Also, because of the strict sterility requirements for all injections, they are more expensive than other dosage forms and require competent trained personnel for their proper administration.

Dosage Forms Applicable

Pharmaceutically, injectable preparations are usually either sterile suspensions or solutions of a drug substance in water or in a suitable vegetable oil. Drugs in solution act more rapidly than drugs in suspension, with an aqueous vehicle providing faster action in each instance than an oleaginous vehicle. As in other instances of drug absorption, a drug must be in solution to be absorbed, and a suspended drug must first submit to the dissolution process. Also, because body fluids are aqueous, they are more receptive to drugs in an aqueous vehicle than those in an oily one. For these reasons, the rate of drug absorption can be varied in parenteral products by selective combinations of drug

state and supporting vehicle. For instance, a suspension of a drug in a vegetable oil likely would be much more slowly absorbed than an aqueous solution of the same drug. Slow absorption means prolonged drug action, and when this is achieved through pharmaceutical means, the resulting preparation is referred to as a *depot* or *repository* injection, because it represents a storage reservoir of the drug substance within the body from which it is slowly removed into the systemic circulation. In this regard, even more sustained drug action may be achieved through the use of subcutaneous implantation of compressed tablets, termed pellets that are only slowly dissolved from their site of implantation, releasing their medication at a rather constant rate over a period of several weeks to many months. The repository type of injection is mainly limited to the subcutaneous or intramscular route. It is obvious that drugs injected intraveously do not encounter absorption barriers and thus produce only rapid drug effects. Preparations for intravenous injection must not interfere with the blood components or with circulation and therefore, with few exceptions, are aqueous solutions.

Subcutaneous Injections

The subcutaneous (hypodermic) administration of drugs involves their injection through the layers of skin into the loose subcutaneous tissue. Subcutaneous injections are prepared as aqueous solutions or as suspensions and are administered in relatively small volumes of 2 mL or less. Insulin is an example of a drug administered by the subcutaneous route. Subcutaneous injections are generally given in the forearm, upper arm, thigh, or buttocks. If the patient is to receive frequent injections, it is best to alterate injection sites to reduce tissue irritation. After injection, the drug comes into the immediate vicinity of blood capillaries and permeates them by diffusion or filtration. The capillary wall is an example of a membrane that behaves as a lipid pore barrier, with lipid-soluble substances penetrating the membrane at rates varying with their oil/water partition coefficients. Lipid-insoluble (generally more water-soluble) drugs penetrate the capillary membrane at rates which appear to be inversely related to their molecular size, with smaller molecules penetrating much more rapidly than larger ones. All substances, whether lipid-soluble or not, cross the capillary membrane at rates that are much more rapid than the rates of their transfer across other body membranes. The blood supply to the site of injection is an important factor in considering the rate of drug absorption, conse-

quently the more proximal capillaries are to the site of injection, the more prompt will be the drug's entrance into the circulation. Also, the more capillaries, the more surface area for absorption, and the faster the rate of absorption. Some substances have the capability of modifying the rate of drug absorption from a subcutaneous site of injection. The addition of a vasconstrictor to the injection formulation (or its prior injection) will generally diminish the rate of drug absorption by causing constriction of the blood vessels in the area of injection and thereby reducing blood flow and the capacity for absorption. This principle is used in the administration of local anesthetics by employing the vasoconstrictor epinephrine. Conversely, vasodilators may be used to enhance subcutaneous absorption by increasing blood flow to the area. Physical exercise can also influence the absorption of drug from an injection site. Diabetic patients who rotate subcutaneous injection sites and then do physical exercise, e.g., jogging, must realize the onset of insulin activity might be influenced by the selected site of administration. Because of the movement of the leg and blood circulation to it during running, the absorption of insulin from a thigh injection site would be expected to be faster than that from an abdominal injection site.

Intramuscular Injections

Intramuscular injections are performed deep into the skeletal muscles, generally the gluteal or lumbar muscles. The site is selected where the danger of hitting a nerve or blood vessel is minimal. Aqueous or oleaginous solutions or suspensions may be used intramuscularly. Certain drugs, because of their inherent low solubilities, provide sustained drug action after an intramuscular injection. For instance, one deep intramuscular injection of a suspension of penicillin G benzathine results in effective blood levels of the drug for seven to ten days.

Drugs that are irritating to subcutaneous tissue are often administered intramuscularly. Also, greater volumes (2 to 5 mL) may be administered intramuscularly than subcutaneously. When a volume greater than 5 mL is to be injected, it is frequently administered in divided doses using two injection sites. Injection sites are best rotated when a patient is receiving repeated injections over a period of time.

Intravenous Injections

In the intravenous administration of drugs, an aqueous solution is injected directly into the vein at a rate commensurate with efficiency, safety, comfort to the patient, and the desired duration of drug

response. Drugs may be administered intravenously as a single, small-volume injection or as a large volume, slow intravenous drip infusion (as is common following surgery). Intravenous injection allows the desired blood level of drug to be achieved in an optimal and quantitative manner. Intravenous injections are usually made into the veins of the forearm and are especially useful in emergency situations where immediate drug response is desired. It is essential that the drug be maintained in solution after injection and not be precipitated within the circulatory system, an event that might produce emboli. Because of a fear of the development of pulmonary embolism, oleaginous bases are not usually intravenously administered. However, an intravenous fat emulsion is used therapeutically as a caloric source for patients receiving parenteral nutrition whose caloric requirements cannot be met by glucose. It may be administered either through a peripheral vein or a central venous catheter at a distinct rate to help prevent the occurrence of untoward reactions.

Intradermal Injections

These injections are administered into the corium of the skin, usually in volumes of about a tenth of a milliliter. Common sites for the injection are the arm and the back. The injections are frequently performed as diagnostic measures, as in tuberculin and allergy testing.

Epicutaneous Route

Drugs are administered topically, or applied to the skin, for their action at the site of application or for systemic drug effects.

Drug absorption via the skin is enhanced if the drug substance is in solution, if it has a favorable lipid/water partition coefficient, and if it is a non-electrolyte. Drugs that are absorbed enter the skin by way of the pores, sweat glands, hair follicles, sebaceous glands, and other anatomic structures of the skin's surface. Because blood capillaries are present just below the epidermal cells, a drug that penetrates the skin and is able to traverse the capillary wall finds ready access to the general circulation.

Among the few drugs currently employed topically to the skin surface for percutaneous absorption and systemic action are nitroglycerin (antianginal), nicotine (smoking cessation), estradiol (estrogenic hormone), clonidine (antihypertensive), and scopolamine (antinausea/antimotion sickness). Each of these drugs is available for use in the form of transdermal delivery systems fabricated

as an adhesive disc or patch which slowly releases the medication for percutaneous absorption. Additionally, nitroglycerin is available in an ointment form for application to the skin's surface for systemic absorption. Nitroglycerin is used therapeutically for ischemic heart diease, with the transdermal dosage forms becoming increasingly popular because of the benefit in patient compliance through their long-acting (24 hours) characteristics. The nitroglycerin patch is generally applied to the arm or chest, preferably in a hair-free or shaven area. The transdermal scopolamine sytem is also in the form of a patch to be applied to the skin; in this case, behind the ear. The drug system is indicated for the prevention of nausea and vomiting associated with motion sickness. The commercially available product is applied to the postauricular area several hours before need (as prior to an air or sea trip) where it releases its medication over a period of 3 days. The concepts of transdermal therapeutic systems are discussed further in Chapter 10.

For the most part, pharmaceutical preparations applied to the skin are intended to serve some local action and as such are formulated to provide prolonged local contact with minimal absorption. Drugs applied to the skin for their local action include antiseptics, antifungal agents, anti-inflammatory agents, local anesthetic agents, skin emollients, and protectants, against environmental conditions, as the effects of the sun, wind, pests, and chemical irritants. For these purposes, drugs are most commonly administered in the form of ointments and related semisolid preparations such as creams and pastes, as solid dry powders, aerosol sprays or as liquid preparations such as solutions and lotions.

Pharmaceutically, ointments, creams, and pastes are semisolid preparations in which the drug is contained in a suitable base (ointment base), which is itself semisolid and either hydrophilic or hydrophobic in character. These bases play an important role in the proper formulation of semisolid preparations, and there is no single base universally suitable as a carrier of all drug substances or for all therapeutic indications. The proper base for a drug must be determined individually to provide the desired drug release rate, staying qualities after application, and texture. Briefly, *ointments* are simple mixtures of drug substances in an ointment base, whereas *creams* are semisolid emulsions and are less viscid and lighter than ointments. Creams are considered to have greater esthetic appeal due to their nongreasy character and their ability to "vanish" into the skin upon rubbing. *Pastes* contain more solid materials than do ointments and are

therefore stiffer and less penetrating. Pastes are usually employed for their protective action and for their ability to absorb serous discharges from skin lesions. Thus when protective rather than therapeutic action is desired, the formulation pharmacist will favor a paste, but when therapeutic action is required, he will prefer ointments and creams. Commerically, many therapeutic agents are prepared in both ointment and cream form and are dispensed and used according to the particular preference of the patient and the prescribing practitioner.

Medicinal powders are intimate mixtures of medicinal substances usually in an inert base as talcum powder. Depending upon the particle size of the resulting blend, the powder will have varying dusting and covering capabilities. In any case, the particle size should be small enough to ensure against grittiness and consequent skin irritation. Powders are most frequently applied topically to relieve such conditions as diaper rash, chafing, and athlete's foot.

When topical application is desired in liquid form other than solution, lotions are most frequently employed. *Lotions* are suspensions of solid materials in an aqueous vehicle, although certain emulsions and even some true solutions have been designated as lotions because of either their appearance or application. Lotions may be preferred over semisolid preparations because of their nongreasy character and their increased spreadability over large areas of skin.

Ocular, Oral, and Nasal Routes

Drugs are frequently applied topically to the eye, ear, and the mucous membranes of the nose. In these instances, ointments, suspensions, and solutions are generally employed. Ophthalmic solutions and suspensions are sterile aqueous preparations with other quantities essential to the safety and comfort of the patient. Ophthalmic ointments must be sterile, and also free of grittiness. Innovative new delivery systems for ophthalmic drugs continue to be investigated. One dosage form, the Ocusert, is an elliptically shaped unit designed for continuous release of pilocarpine following its placement into the cul-de-sac of the eye. Further, case reports of the ability of soft contact lenses to absorb drug from the eye have spawned research in the development of soft contact lenses impregnated with drug for therapeutic application in the eye. Nasal preparations are usually solutions or suspensions administered by drops or as a fine mist from a nasal spray container. Current research is di-

rected toward the feasibility of the nasal administration of insulin for diabetes mellitus. Otic, or ear preparations are usually viscid so that they have prolonged contact with the affected area. They may be employed simply to soften ear wax, to relieve an earache, or to combat an ear infection. Eye, ear, and nose preparations usually are not used for systemic effects, and although ophthalmic and otic preparations are not usually absorbed to any great extent, nasal preparations *may* be absorbed, and systemic effects after the intranasal application of solution are not unusual.

Other Routes

The lungs provide an excellent absorbing surface for the administration of gases and for aerosol mists of very minute particles of liquids or solids. The gases employed are mainly oxygen and the common general anesthetic drugs administered to patients entering surgery. The rich capillary area of the alveoli of the lungs, which in man covers nearly a thousand square feet, provides rapid absorption and drug effects comparable in speed to those following an intravenous injection. In the case of drug particles, their size largely determines the depth to which they penetrate the alveolar regions; their solubility, the extent to which they are absorbed. After contact with the inner surface of the lungs, an insoluble drug particle is caught in the mucus and is moved up the pulmonary tree by ciliary action. Soluble drug particles that are approximately 0.5 to 1.0 μ in size reach the minute alveolar sacs and are most prompt and efficient in providing systemic effects. Particles that are smaller than 0.5 μ are expired to some extent, and thus their absorption is not total but variable. Particles from 1 to 10 μ in size effectively reach the terminal bronchioles and to some extent the alveolar ducts and are favored for local therapy. Therefore, in the pharmaceutical manufacture of aerosol sprays for inhalation therapy, the manufacturers not only must attain the proper drug particle size but also must ensure their uniformity for consistent penetration of the pulmonary tree and uniform effects.

In certain instances and for local effects, drugs are inserted into the vagina and the urethra. Drugs are usually presented to the vagina in tablet form, as suppositories, ointments, emulsion foams, gels or solutions, and to the urethra as suppositories or solutions. Systemic drug effects may result after the vaginal or urethral application of drugs due to absorption of the drug from the mucous membranes of these sites.

Fate of Drug after Absorption

After absorption into the general circulation from any route of administration, a drug may become bound to blood proteins and delayed in its passage into the surrounding tissues. Many drug substances may be highly bound to blood protein and others little-bound. For instance, when in the blood stream, naproxen is 99% bound to plasma proteins, penicillin G is 60% bound, amoxicillin only 20% bound, and minoxidil is unbound.

The degree of drug binding to plasma proteins is usually expressed as a percentage or as a fraction (termed *alpha*, or α) of the bound concentration (C_b) to the total concentration (C_t), bound plus unbound (C_u) drug:

$$\alpha = \frac{C_b}{C_u + C_b} = \frac{C_b}{C_t}$$

Thus, if one knows two of the three terms in the equation, the third may be calculated. Drugs having an alpha value of greater than 0.9 are considered highly bound (90%); those drugs with an alpha value of less than 0.2 are considered to be little (20% or less) protein bound. Table 4.9 presents approximate serum protein binding characteristics for representative drugs present in the blood under conditions associated with usual therapy. The drug-protein complex is reversible and involves albumin, although globulins are also involved in the binding of drugs, particularly some of the hormones. The binding of drugs to biologic materials involves the formation of relatively weak bonds (e.g., van der Waals, hydrogen, and ionic bonds). The binding capacity of blood proteins is limited, and once they are saturated, additional drug absorbed into the blood stream remains unbound unless bound drug is released, creating a vacant site for another drug molecule to attach. Any unbound drug is free to leave the blood stream for tissues or cellular sites within the body.

Bound drug is neither exposed to the body's detoxication (metabolism) processes nor is it filtered through the renal glomeruli. Bound drug is therefore referred to as the *inactive* portion in the blood, and unbound drug, with its ability to penetrate cells, is termed the *active* blood portion. The bound portion of drug serves as a drug reservoir or a depot, from which the drug is released as the free form when the level of free drug in the blood no longer is adequate to ensure protein saturation. The free drug may be only slowly released, thereby increasing the duration of the drug's stay in the body. For this reason a drug that is highly protein bound may remain in the body for longer periods of time

Table 4.9. **Examples of Drug Binding to Plasma Proteins**

Drug	Percent Bound
Naproxen (Naprosyn)	>99
Chlorambucil (Leukeran)	>99
Etodolac (Lodine)	>99
Warfarin (Coumadin)	>97
Fluoxetine (Prozac)	>95
Cloxacillin (Tegopen)	>95
Ceftriaxone (Rocephin)	85–95
Cefoperazone (Cefobid)	82–93
Cefonicid (Monocid)	>90
Indomethacine (Indocin)	>90
Spironolactone (Aldactone)	>90
Digitoxin (Crystodigin)	>90
Cyclosporine (Sandimmune)	>90
Sulfisoxazole (Gantrisin)	>85
Diltiazem (Cardizem)	70–80
Penicillin V (Veetids)	>75
Nitroglycerin (Nitro-Bid)	>60
Penicillin G Potassium	>60
Methotrexate	>50
Methicillin (Staphcillin)	>40
Ceftizoxime (Cefizox)	>30
Captopril (Capozide)	25–30
Ciprofloxacin (Cipro)	20–40
Digoxin (Lanoxin)	20–25
Ampicillin (Omnipen)	>20
Amoxicillin (Amoxil)	>20
Metronidazole (Flagyl)	<20
Mercaptopurine (Purinethol)	>19
Cephradine (Velosef)	8–17
Ranitidine (Zantac)	>15
Ceftazidime (Tazicef)	<10
Nicotine (Prostep)	<5
Minoxidil (Loniten)	>0

Average literature values, based on conditions usually associated with drug therapy.

and require less frequent dosage administration than another drug that may be only slightly protein bound and may remain in the body for only a short period of time. Evidence suggests that the concentration of serum albumin decreases about 20% in the elderly. This may be clinically significant for drugs that bind strongly to albumin, e.g., phenytoin, because if there is less albumin available to bind the drug there will be a corresponding increase of the free drug in the body. Without a downward dosage adjustment in an elderly patient, there could be an increased incidence of adverse effects.

A drug's binding to blood proteins may be affected by the simultaneous presence of a second (or more) drug(s). The additional drug(s) may result in

drug effects or durations of drug action quite dissimilar to that found when each is administered alone. Salicylates, for instance, have the effect of decreasing the binding capacity of thyroxin, the thyroid hormone, to proteins. Phenylbutazone is an example of a drug that competitively displaces several other drugs from serum binding sites, including other antiinflammatory drugs, oral anticoagulants, oral antidiabetics, and sulfonamides. Through this action, the displaced drugs become less protein bound and their activity (and toxicity) may be increased. The intensity of a drug's pharmacologic response is related to the ratio of the bound drug *versus* free, active drug, and the therapeutic index of the drug. Warfarin, an anticoagulant is 97% bound to plasma protein leaving 3% in free form to exert its effect. If a second drug, such as naproxen, which is strongly bound to plasma proteins is administered and results in only 90% of the warfarin being bound, this means that 10% of warfarin is now in the free form. Thus, the blood level of the free warfarin (3 to 10%) has tripled and could result in serious toxicity. The displacement of drugs from plasma protein sites is typical in the elderly who normally are maintained on numerous medicines. Coupled with the aforementioned decrease in serum protein through the aging process the addition of a highly protein-bound drug to an elderly patient's existing treatment regimen could pose significant problems if the patient is not monitored carefully for signs of toxicity.

In the same manner as they are bound to blood proteins, drugs may become bound to specific components of certain cells. Thus drugs are not distributed uniformly among all cells of the body, but rather tend to pass from the blood into the fluid bathing the tissues and may accumulate in certain cells according to their permeability capabilities and chemical and physical affinities. This affinity for certain body sites influences their action, for they may be brought into contact with reactive tissues (their *receptor sites*) or deposited in places where they may be inactive. Many drugs, because of their affinity for and solubility in lipids, are found to be deposited in fatty body tissue, thereby creating a storage place or drug reservoir from which they are slowly released to other tissues.

Drug Metabolism (Biotransformation)

Although some drugs are excreted from the body in their original form, many drugs undergo biotransformation prior to excretion. Biotransformation is a term used to indicate the chemical changes that occur with drugs within the body as they are metabolized and altered by various biochemical mechanisms. The biotransformation of a drug results in its conversion to one or more compounds that are more water soluble, more ionized, less capable of binding to proteins of the plasma and tissues, less capable of being stored in fat tissue, and less able to penetrate cell membranes, and thereby less active pharmacologically. Because of its new characteristics, a drug so transformed is rendered less toxic and is more readily excreted. It is for this reason that the process of biotransformation is also commonly referred to as the "detoxification" or "inactivation" process. (However, sometimes the metabolites are more active than the parent compound; see *prodrugs*, following.)

The exact metabolic processes (pathways) by which drugs are transformed represent an active area of biomedical research. Much work has been done with the processes of animal degradation of drugs and in many instances the biotransformation in the animal is thought to parallel that in man. There are four principal chemical reactions involved in the metabolism of drugs: oxidation, reduction, hydrolysis, and conjugation. Most oxidation reactions are catalyzed by enzymes (oxidases) bound to the endoplasmic reticulum, a tubular system within liver cells; only a small fraction of drugs are metabolized by reduction, through the action of reductases, present in the gut and liver; esterases in the liver participate in the hydrolytic breakdown of drugs containing ester groups as well as amides; glucuronide conjugation is the most common pathway for drug metabolism, through combination of the drug with glucuronic acid, forming ionized compounds that are easily eliminated (2). Other metabolic processes, including methylation and acylation conjugation reactions, occur with certain drugs to foster elimination.

In recent years, much interest has been shown in the metabolites of drug biotransformation. Certain metabolites may be as active or even more active pharmacologically than the original compound. Occasionally an active drug may be converted into an active metabolite, which must be excreted as such or undergo further biotransformation to an inactive metabolite, e.g., amitriptyline to nortriptyline. In other instances of drug therapy, an inactive parent compound, referred to as a *prodrug*, may be converted to an active therapeutic agent by chemical transformation in the body. An example is the prodrug enalapril (Vasotec), which after oral administration is hydrolyzed to enalaprilat, an active angiotensin-converting enzyme (ACE) inhibitor used

in the treatment of hypertension. Enalaprilat itself is poorly absorbed when taken orally (and thus the prodrug) but may be administered intravenously in aqueous solution. The use of these active metabolites as "original" drugs represents a new area of drug investigation and a vast reservoir of potential therapeutic agents.

Several examples of biotransformations occurring within the body are as follows:

(1) Acetaminophen $\xrightarrow{\text{conjugation}}$ Acetaminophen glucuronide
     (active)   (inactive)

(2) Amoxapine $\xrightarrow{\text{oxidation}}$ 8-hydroxy-amoxapine
     (active)   (inactive)

(3) Procainamide $\xrightarrow{\text{hydrolysis}}$ p-Aminobenzoic acid
     (active)   (inactive)

(4) Nitroglycerin $\xrightarrow{\text{reduction}}$ 1–2 and 1–3 dinitroglycerol
     (active)   (inactive)

Some parent compounds undergo full, partial, or no biotransformation following administration. Lisinopril (Zestril), for example, does not undergo metabolism and is excreted unchanged in the urine. On the other hand, verapamil (Calan) metabolizes to at least 12 metabolites, the most prevalent of which is norverapamil. Norverapamil has 20% of the cardiovascular activity of the parent compound. Diltiazem (Cardizem) is partially metabolized (about 20%) to desacetyldiltiazem, which has 10–20% the coronary vasodilator activity of the parent compound. Indomethacin (Indocin) is metabolized in part to desmethyl, desbenzoyl, and desmethyldesbenzoyl metabolites. Propoxyphene napsylate (Darvon N) is metabolized to norpropoxyphene, which has less central nervous system depressant action than the parent compound but greater local anesthetic effects. The majority of metabolic transformations takes place in the liver, with some drugs as diltiazem and verapamil undergoing extensive first-pass effects. Other drugs, such as terazosin (Hytrin), undergo minimal first-pass metabolism effects. The excretion of both drug and metabolites takes place primarily, but to varying degrees, via the urine and feces. For example, indomethacin and its metabolites are excreted primarily (60%) in the urine, with the remainder in the feces, whereas terazosin and its metabolites are excreted largely (60%) through the feces, and the remainder in the urine.

It is important to mention that several factors influence drug metabolism. For example, there are marked differences between *species* in pathways of hepatic metabolism of a given drug. Species differences make it extremely difficult to extrapolate from one species to another, e.g., laboratory animals to humans. Furthermore, there are many examples of *interindividual variations* in hepatic metabolism of drugs within one species. Genetic factors are involved in the determination of the basal activity of the drug metabolizing enzyme systems. Thus, there can be marked intersubject variation in the rate at which certain individuals metabolically handle drugs. Because of this variation, a physician must individualize therapy to maximize the chances for a constructive therapeutic outcome with minimal toxicity. Studies in humans have demonstrated that these differences have occurred within the cytochrome P-450 genetic codes for a family of isoenzymes responsible for drug metabolism.

Age of the patient is another significant factor that influences drug metabolism. Although pharmacokinetic calculations have not been able to develop a specific correlative relationship with age, it is known, for example, that the ability to metabolize drugs decreases at the extremes of the age scale, i.e., elderly, neonate. Liver blood flow is reduced by aging at about 1% per year beginning around age 30.[9] This decreased blood flow to the liver reduces the capacity for hepatic drug metabolism and elimination. For example, the half-life of chlordiazepoxide increases from about 6 hours at age 20 to about 36 hours at age 80. Further, an immature hepatic system disallows the effective metabolism of drugs by the newborn or premature infant. As mentioned earlier, the half-life of theophylline ranges between 14 to 58 hours in the premature infant to 2.5 to 5 hours in young children between the ages of 1 to 4 whose liver enzyme systems are mature.

Diet has also been demonstrated to modify the metabolism of some drugs. For example, the conversion of an asthmatic patient from a high to a low protein diet will increase the half-life of theophylline. It has also been demonstrated that the production of polycyclic hydrocarbons by the charcoal broiling of beef enhances the hepatic metabolism and shortens the plasma half-life of theophylline. It is conceivable that this effect could also occur with drugs that are metabolized in similar fashion to theophylline. Diet type, e.g., starvation, certain vegetables (brussels sprouts, cabbage, broccoli), has been shown to influence the metabolism of certain drugs. Lastly, it is important to mention that exposure to other drugs or chemicals, e.g., pes-

ticides, alcohol, nicotine, and the presence of disease states, e.g., hepatitis, have all demonstrated an influence on the drug metabolism and consequently the pharmacokinetic profile of certain drugs.

Excretion of Drugs

The excretion of drugs and their metabolites terminates their activity and presence in the body. They may be eliminated by various routes, with the kidney playing the dominant role by eliminating drugs via the urine. Drug excretion with the feces is also important, especially for drugs that are poorly absorbed and remain in the gastrointestinal tract after oral administration. Exit through the bile is significant only when the drug's reabsorption from the gastrointestinal tract is minimal. The lungs provide the exit for many volatile drugs through the expired breath. The sweat glands, saliva, and milk play only minor roles in drug elimination. However, it should be recognized that if a drug gains access to the milk of a mother during lactation, it could easily exert its drug effects in the nursing infant. Examples of drugs that do enter breast milk and may be passed on to nursing infants include theophylline, penicillin, reserpine, codeine, meperidine, barbiturates, diltiazem, and thiazide diuretics. It is generally good practice for the mother to abstain from taking medication during the period of time she is nursing her infant. If she must take medication, she should abide by a dosage regimen and nursing schedule that permit her own therapy yet ensure the safety of her child. Not all drugs gain entrance into the milk; nevertheless, caution is advisable. Manufacturers' package inserts contain product-specific information (usually in the "Precautions" section) on drug migration into breast milk.

The unnecessary use of medications during the early stages of pregnancy is likewise restricted by physicians, because certain drugs are known to have the ability to cross the placental barrier and gain entrance to the tissues and blood of the fetus. Among the many drugs known to do so after administration to an expectant mother are all of the anesthetic gases, many barbiturates, sulfonamides, salicylates, and a number of other potent agents like quinine, meperidine, and morphine, the latter two drugs being narcotic analgesics with great addiction liabilities. In fact, it is not unusual for a newborn infant to be born an addict due to the narcotic addiction of its mother and the passage of the narcotic drugs across the placental barrier.

The kidney, as the main organ for the elimination of drugs from the body, must be functioning adequately if drugs are to be efficiently eliminated. For instance, elimination of digoxin occurs largely through the kidney according to first-order kinetics; that is, the quantity of digoxin eliminated at any time is proportional to the total body content. Renal excretion of digoxin is proportional to the glomerular filtration rate which when normal results in a digoxin half-life that may range from 1.5 to 2.0 days. When the glomerular filtration rate becomes impaired or disrupted, however, as in an anuric patient, the elimination rate decreases. Consequently, the half-life of digoxin may be between 4 to 6 days. Because of this prolongation of digoxin's half-life, the dosage of the drug must be decreased or the dosage interval prolonged. Otherwise, the patient will experience digoxin toxicity. The degree of impairment can be estimated by measurements of glomerular filtration rates, most often by creatinine clearance determination. Usually, however, this is not feasible and the patient's serum creatinine value is used within appropriate pharmacokinetic equations to help determine a drug's dosage regimen.

Some drugs may be reabsorbed from the renal tubule even after having been sent there for excretion. Because the rate of reabsorption is proportional to the concentration of drug in unionized form, it is possible to modify this rate by adjusting the pH of the urine. By acidifying the urine, as with the oral administration of ammonium chloride, or by alkalinizing it, as with the administration of sodium bicarbonate, one can increase or decrease the ionization of the drug and thereby alter its prospect of being reabsorbed. Alkalinization of the urine has been shown to enhance the urinary excretion of weak acids such as salicylates, sulfonamides, and phenobarbital. The opposite effect can be achieved by acidifying the urine. Thus, the duration of a drug's stay within the body may be markedly altered by changing the pH of the urine. Some foods, such as cranberry juice, can also serve to acidify the urine and may alter drug excretion rates.

The urinary excretion of drugs may also be retarded by the concurrent administration of agents capable of inhibiting their tubular secretion. A well-known example is the use of probenecid to inhibit the tubular secretion of various types of penicillin, thereby reducing the frequency of dosage administrations usually necessary to maintain adequate therapeutic blood levels of the antibiotic drug. In this particular instance, the elevation of penicillin blood levels, by whatever route the antibiotic is administered, to twofold and even fourfold levels has been demonstrated by adjuvant therapy with probenecid. The effects are completely reversible

upon withdrawal of the probenecid from concomitant therapy.

The fecal excretion of drugs appears to lag behind the rate of urinary excretion partly because a day or so elapses before the feces reach the rectum. It should be easily seen that drugs administered orally for local activity within the gastrointestinal tract and not absorbed will be eliminated completely via the feces. Unless a drug is particularly irritating to the gastrointestinal tract, there is generally no urgency in removing unabsorbable drugs from the system by means other than the normal defecation process. Some drugs that are only partially absorbed after oral administration will naturally be partly eliminated through the rectum.

Pharmacokinetic Principles

This section introduces the concept of pharmacokinetics and how it interrelates the various processes that take place when one administers a drug to a patient, i.e., absorption, distribution, metabolism, excretion. It is not intended to be comprehensive, and thus for further information about the subject the reader is referred to other appropriate literature sources.

A problem encountered when one needs to determine a more accurate dosage of a drug or a more meaningful interpretation of a biologic response to a dose is the inability to determine the drug concentration at the active site in the body. Consequently, to solve this dilemma, the concept of compartmental analysis is used within the discipline of pharmacokinetics in an attempt to quantitatively define what has become of the drug as a function of time from the moment it is administered until it is no longer in the body. Pharmacokinetic analysis utilizes mathematical models to simplify or simulate the disposition of the drug in the body. The idea is to begin with a simple model and then modify as necessary. The principal assumption is that the human body may be represented by one or more *compartments* or pools in which a drug resides in a dynamic state for a short period of time. A compartment is a hypothetical space bound by an unspecified membrane across which drugs are transferred (Fig. 4.13). The transfer of drugs into and out of this compartment is indicated by arrows that point in the direction of drug movement into or out of the compartment. The rate at which a drug is transferred throughout the system is designated by a symbol that usually represents an exponential rate constant. Typically, the letter K or k with numerical or alpha-numerical subscripts is utilized.

There are several assumptions associated with
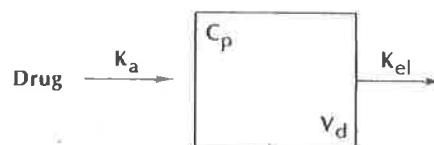
Where:
C_p is the drug concentration in plasma
V_d is the volume of the compartment or volume of distribution

Fig. 4.13 *Schematic of a one-compartment system.*

modeling of drug behavior once in the body. It is assumed that the volume of each compartment remains constant. Thus, an equation that describes the time course of the amount of drug in the compartment can be converted to an equation that depicts the time course of the drug concentration in the compartment by dividing both sides of the equation by the volume of the compartment. Secondly, it is assumed that once a drug enters the compartment it is instantaneously and uniformly distributed throughout the entire compartment. Thus, it is assumed that a sampling of any one portion of the compartment will yield the drug concentration of the entire compartment.

In compartment models it is assumed that drug passes freely into and out of compartments. Thus, these compartmental systems are known as "open" systems. Typically, the process of drug transport between compartments follows first-order kinetics, herein a constant fraction of drug present is eliminated per unit time, and can be described by ordinary differential equations. In these linear systems the time constants that describe the rate at which the plasma or blood concentration curve of a drug decays are independent of the dose of the drug, the volume of distribution of the drug and the route of administration.

The simplest pharmacokinetic model is the single compartment *open-model system* (Figure 4.13). This model depicts the body as one compartment characterized by a certain volume of distribution (V_d) that remains constant. Each drug has its own distinct volume of distribution and this can be influenced by certain patient factors, e.g., age, disease state status. In this scheme a drug can be instantaneously introduced into the compartment, i.e., rapid intravenous administration, or gradually, e.g., oral administration. In the former example it is assumed that the drug distributes immediately to tissues with instantaneous attainment of equilibrium. In

the latter example, the drug is absorbed at a certain rate and is characterized by the rate constant K_a. Lastly, the drug is eliminated from the compartment at a certain rate that is characterized by a rate constant K_{el}.

It is relevant at this point to consider the *volume of distribution*, V_d. The volume of distribution is a proportionality constant and is a term that refers to the volume into which the total amount of drug in the body would have to be uniformly distributed to provide the concentration of drug actually measured, e.g., in plasma, in blood. This term can be misleading because it does not represent a specific body fluid or volume. It is influenced by the plasma-protein binding and tissue binding characteristics of a drug. These then influence the distribution of the drug between plasma water, extracellular fluid, intracellular fluid and total body water. Further, because a drug can partition between fat and water according to its unique partition coefficient, this can also influence the volume of distribution. Because of these phenomena, pharmacokineticists find it convenient to describe a drug distribution in terms of compartment models.

To determine the rate of drug transfer into and out of the compartment, plasma, serum, or blood samples are drawn at predetermined times after the drug is administered and analyzed for drug concentration. Once a sufficient number of experimental data points is determined, these are plotted on semi-logarithmic paper and an attempt is made to fit the experimental points with the smoothest curve to fit these points. Figure 4.14 dep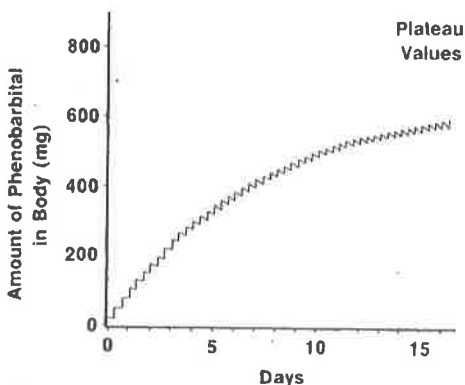icts the plasma concentration *versus* time profile for a hypothetical drug following rapid intravenous injection of a bolus dose of the drug with instantaneous distribution. For drugs whose distribution follows first-order, one-compartment pharmacokinetics, a plot of the logarithm of the concentration of drug in the plasma (or blood) versus time will yield a straight line. The equation that describes the plasma decay curve is:

$$C_p = C_p^0 \, e^{-K_{el}t} \qquad \text{(Equation 4.1)}$$

where K_{el} is the first-order rate of elimination of the drug from the body, C_p is the concentration of the drug at a time equal to t, and C_p^0 is the concentration of drug at time equal to zero, when all the drug administered has been absorbed but none has been removed from the body through elimination mechanisms, e.g., metabolism, renal excretion. The apparent first-order rate of elimination, K_{el}, is usually the sum of the rate constants of a number of individual processes, e.g., metabolic transformation, renal excretion.

For the purpose of pharmacokinetic calculation it is simpler to convert Equation 4–1 to natural logs:

$$\text{Ln } C_p = \text{Ln } C_p^0 - K_{el}\,(t) \qquad \text{(Equation 4.2)}$$

and then to log base$_{10}$:

$$\text{Log } C_p = \text{Log } C_p^0 - K_{el}\,(t)/2.303 \qquad \text{(Equation 4.3)}$$

Equation 4–3 is then thought of in terms of the Y-intercept form:

$$Y = b + m \times$$
$$\text{Log } C_p = \text{Log } C_p^0 - K_{el}/2.303\,(t)$$

and interpreted as such in the semi-logarithmic plot illustrated in Figure 4.14. Most drugs administered orally can be adequately described using a one-compartment model, whereas drugs administered by rapid intravenous infusion are usually best described by a two-compartment or three-compartment model system.

Assuming that a drug's volume of distribution, V_d, is constant within this system, the total amount of drug in the body (Q_b) can be calculated from the following equation:

$$Q_b = [C_p^0]\,[V_d] \qquad \text{(Equation 4.4)}$$

Fig. 4.14 *Plot of the plasma concentration-time data. (Reprinted with permission from Rowland M, Tozer TN. Clinical Pharmacokinetics. 2nd Ed., Philadelphia: Lea & Febiger, 1989).*
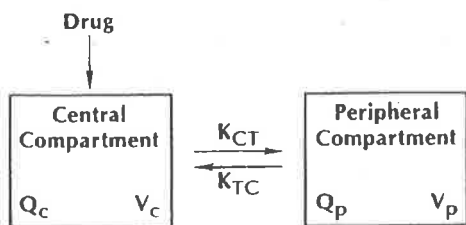
Usually, C_p^0 is determined by extrapolating the drug-concentration time plot back to time zero.

In this simple one-compartment system it is assumed that the administered drug is confined to

the plasma (or blood) and then excreted. Drugs that exhibit this behavior will have small volumes of distribution. For example, a drug such as warfarin which is extensively bound to plasma albumin will have a volume of distribution equivalent to that of plasma water, about 2.8 liters in an average 70 kg adult. Some drugs, however, will initially be distributed at somewhat different rates in various fluids and tissues. Consequently, these drugs' kinetic behavior can best be illustrated by considering an expansion of the one-compartment system to the *two compartment model* (Fig. 4.15).

In the two-compartment system, a drug enters into and is instantaneously distributed throughout the central compartment. Its subsequent distribution into the second or peripheral compartment is slower. For simplicity, on the basis of blood perfusion and tissue-plasma partition coefficients for a given drug, various tissues and organs are considered together and given the designation as central compartment or peripheral compartment. The central compartment is usually considered to include the blood, the extracellular space, and organs with good blood perfusion, e.g., lungs, liver, kidneys, heart. The peripheral compartment is usually constituted by those tissues and organs which are poorly perfused by blood, e.g., skin, bones, fat.

Figure 4.16 depicts the plasma-drug concentration versus time plot for a rapidly administered intravenous dose of a hypothetical drug which exhibits kinetic behavior exemplifying a two-compartment system. Note the initial steep decline of the plasma drug concentration curve. This typifies the distribution of the drug from the central compartment to the peripheral compartment.
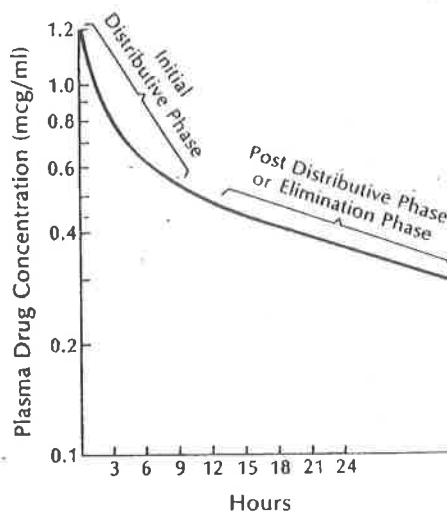

Fig. 4.16 *A semilogarithmic plasma concentration versus time plot of an intravenously administered drug that follows first order, two-compartment pharmacokinetics.*

During this phase the drug concentration in the plasma will decrease more rapidly than in the post-distributive phase, i.e., elimination phase. Whether or not this distributive phase is apparent will depend upon the timing of the plasma samples, particularly in the time immediately following administration. A distributive phase can be very short, a few minutes, or last for hours and even days.

A semi-logarithmic plot of the plasma concentration versus time after rapid intravenous injection of a drug which is best described by a two-compartment model system can often be resolved into two linear components. This procedure can be performed by the method of residuals (or feathering), Figure 4.17. In this procedure, a straight line is fitted through the tail of the original curve and extrapolated back to the Y-axis (the value obtained is B). A plot is then made of the absolute difference values of the original curve and the resultant extrapolated straight line. The slope of the feathered line ($-a/2.303$) and the extrapolated line ($-b/2.303$) and the intercepts, A and B, are determined. Then the following equation is constructed that describes a two-compartment system:
(Equation 4–5)

$$C_p = Ae^{-at} + Be^{-bt}$$

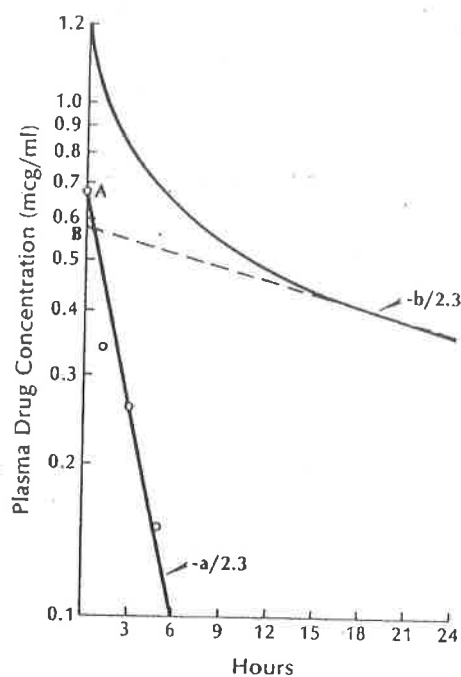This is a bi-exponential equation which describes the two-compartment system.

Where:
Q_c = Quantity of drug in central compartment
V_c = Volume of the central compartment
Q_p = Quantity of drug in peripheral compartment
V_p = Volume of the peripheral compartment

Fig. 4.15 *Schematic of a two-compartment system.*

Fig. 4.17 *The logarithm of the drug concentration in plasma plotted versus time (solid line) after intravenous administration of a drug whose disposition can be described by a two-compartment model.*

In this scheme, the slope of the line, i.e., −a/2.303, obtained from feathering yields the distributive rate of the drug. The slope of the terminal linear phase or elimination phase, i.e., −b/2.303, describes the rate of loss of the drug from the body, and usually is considered to be a reflection of the metabolic processes and renal elimination from the body. Appropriate pharmacokinetic formulas allow the clinician to calculate the various volumes of distribution and rates of distribution and elimination for drugs whose pharmacokinetic behavior is exemplified by the two-compartment system.

Half-Life

The half-life ($T_{1/2}$) of a drug describes the time required for a drug's blood or plasma concentration to decrease by one half. This fall in drug concentration is a reflection of metabolic processes and/or excretion, e.g., renal, fecal. The biological half-life of a drug in the blood may be determined graphically off of a pharmacokinetic plot of a drug's blood-concentration time plot, typically after intra-

venous administration to a sample population. The amount of time required for the concentration of the drug to decrease by one half is considered its half-life. The half-life can also be mathematically determined. Recall Equation 4–3 and rearrange the equation as follows:

$$\frac{K_{el}\, t}{2.303} = Log\, C_p^0 - Log\, C_p = Log\, \frac{C_p^0}{C_p}$$

(Equation 4.6)

Then, if it assumed that C_p is equal to one-half of C_p^0, the equation will become:

$$\frac{K_{el}\, t}{2.303} = Log\, \frac{C_p^0}{0.5\, C_p^0} = Log\, 2$$

(Equation 4.7)

Thus,

$$t_{1/2} = \frac{2.303\, Log\, 2}{K_{el}} = \frac{0.693}{K_{el}}$$

(Equation 4.8)

If this latter equation is rearranged, the half-life finds utility in the determination of drug elimination from the body, provided of course that the drug follows first-order kinetics. Rearranging the prior equation:

$$K_{el} = \frac{0.693}{t_{1/2}}$$

(Equation 4.9)

Elimination rate constants are reported in time^{-1}, e.g., minutes^{-1}, hours^{-1}. Thus, an elimination constant of a drug is 0.3 hr^{-1} indicates that 30% of the drug is eliminated per hour.

The half-life varies widely between drugs; for some drugs it may be a few minutes, whereas for other drugs it may be hours or even days (Table 4.10). Data on a drug's biologic half-life are useful in determining the most appropriate dosage regimen to achieve and maintain the desired blood level of drug. Such determinations usually result in such recommended dosage schedules for a drug, as the drug to be taken every 4 hours, 6 hours, 8 hours, etc. Although these types of recommendations generally suit the requirements of most patients, they do not suit all patients. The most exceptional patients are those with reduced or impaired ability to metabolize or excrete drugs. These patients, generally suffering from liver dysfunction or kidney disease, retain the administered drug in the blood or tissues for extended periods of time due to their decreased ability to eliminate the drug. The resulting extended biologic half-life of the drug generally ne-

Table 4.10.   Some Elimination Half-Life Values

Drug Substance/Product	Elimination Half-Life* ($t_{1/2}$)
Acetaminophen (Tylenol)	1–4 hours
Amoxicillin (Amoxil)	1 hour
Butabarbital Sodium (Butisol Sodium)	100 hours
Cimetidine (Tagamet)	2 hours
Digitoxin (Crystodigin)	7–9 days
Digoxin (Lanoxin)	1.5–2 days
Diltiazem (Cardizem)	2.5 hours
Ibuprofen (Motrin)	1.8–2 hours
Indomethacin (Indocin)	4.5 hours
Lithium Carbonate (Eskalith)	24 hours
Nitroglycerin (Tridil)	3 minutes[†]
Phenytoin Sodium (Dilantin)	7–29 hours
Pentobarbital Sodium (Nembutal Sodium)	15–50 hours
Propoxyphene (Darvon)	6–12 hours
Propranolol HCl (Inderal)	4 hours
Ranitidine HCl (Zantac)	2.5–3 hours
Theophylline (Theo-Dur)	3–15 hours
Tobramycin Sulfate (Nebcin)	2 hours
Tolbutamide (Orinase)	4.5–6.5 hours

*Mean, average, or value ranges, taken from product information found in *Physicians' Desk Reference*, 52nd ed., 1998, Medical Economics Data, Montvale, New Jersey. Half-life values may vary depending upon patient characteristics (age, liver or renal function, smoking habits, etc.), dose levels administered, and routes of administration.

[†]After intravenous infusion; nitroglycerin is rapidly metabolized to dinitrates and mononitrates.

cessitates an individualized dosage regimen calling for less frequent drug administration than that called for in patients with normal processes of drug elimination, or a maintenance of the usual dosage schedule, but a decrease in the amount of drug administered.

The drug digoxin presents a good example of a drug having a half-life which is affected by the patient's pathologic condition. Digoxin is eliminated in the urine. Renal excretion of digoxin is proportional to glomerular filtration rate. In subjects with normal renal function, digoxin has a half-life of 1.5 to 2.0 days. In anuric patients (absence of urine formation), the half-life may be prolonged to 4 to 6 days. Theophylline also demonstrates differing half-lives dependent upon certain patient populations. In premature infants with immature liver enzyme systems in the cytochrome P-450 family, the half-life of theophylline ranges from 14 to 58 hours, whereas in young children between the ages of 1 to 4 whose liver enzyme systems are more mature the theophylline half-life ranges between 2 to 5.5 hours.

In adult nonsmokers, the half-life ranges from 6.1 to 12.8 hours, whereas in adult smokers the average half-life of theophylline is 4.3 hours. The increase in theophylline clearance from the body among smokers is believed to be due to an induction of the hepatic metabolism of theophylline. The half-life of theophylline is decreased and total body clearance is enhanced to such a degree in smokers that these individuals may actually require a 50 to 100% increase in theophylline dosage to produce effective therapeutic results. Between 3 months and 2 years may actually be required to normalize the effect of smoking on theophylline metabolism in the body once the patient stops smoking. Because theophylline is metabolized in the liver, the half-life of theophylline will be extended in liver disease. For example, in one study 9 patients with decompensated cirrhosis, the average theophylline half-life was 32 hours.

The half-life of a drug in the blood stream may also be affected by a change in the extent to which it is bound to blood protein or cellular components. Such a change in a drug's binding pattern may be brought about by the administration of a second drug having a greater affinity than the first drug for the same binding sites. The result is the displacement of the first drug from these sites by the second drug and the sudden availability of free (unbound) drug which may pass from the blood stream to other body sites, including those concerned with its elimination. It should be noted that the displacement of one drug from its binding sites by another is generally viewed as an undesired event, since the amount of free drug resulting is greater than the level normally achieved during single drug therapy and may result in untoward drug effects.

Concept of Clearance

The three main mechanisms by which a drug is removed or cleared from the body include (1) the hepatic metabolism, i.e., hepatic clearance, Cl_h, of a drug to either an active or inactive metabolite, (2) the renal excretion, i.e., renal clearance, Cl_r, of a drug unchanged in the urine, and (3) elimination of the drug into the bile and subsequently into the intestines for excretion in feces. An alternate way to express this removal or elimination from the body is to use total body clearance (Cl_B), which is defined as the fraction of the total volume of distribution that can be cleared per unit time. Because most drugs when administered will undergo one or more of these processes, the total body clearance, Cl_B, of a drug is the sum of these clearances, usu-

ally hepatic, Cl_h and renal clearances Cl_r. Clearance via the bile and feces is usually not significant for most drugs.

These processes of elimination within the body work together and consequently a drug that is eliminated by renal excretion and hepatic biotransformation will have an overall rate of elimination. K_{el}, that is the sum of the renal excretion, k_u, and hepatic biotransformation, k_m. In the one compartment model described earlier, total body clearance is the product of the volume of distribution, V_d, and the overall rate of elimination, k_{el}:

$$Cl_B = V_d \times k_{el} \qquad \text{(Equation 4.10)}$$

But, recall that k_{el} equals $0.693/t_{1/2}$. If this is substituted into Equation 4–10, and one solves for the half-life, $t_{1/2}$, the following equation is obtained:

$$t_{1/2} = \frac{0.693\,V_d}{Cl_B} \qquad \text{(Equation 4.11)}$$

Recall that total body clearance is a function of one or more processes, thus if a drug were eliminated from the body through hepatic biotransformation and renal clearance, Equation 4–11 becomes:

$$t_{1/2} = \frac{0.693\,V_d}{Cl_h + Cl_r} \qquad \text{(Equation 4.12)}$$

Thus, a drug's half-life is directly proportional to the volume of distribution and inversely proportional to the total body clearance which is comprised of hepatic and renal clearances. Illustratively, if one considers infants and children who exhibit larger volumes of distribution and have lower clearance values, drugs will usually have greater half-lives than that exhibited in adults.

A decrease in the hepatic or renal clearances will prolong the half-life of a drug. This typically occurs for example in renal failure, and consequently, if one can estimate the percentage decrease in excretion due to renal failure one can use Equation 4–12 to calculate the new half-life of the drug in the patient. Thus, an adjusted dosage regimen can then be calculated to decrease the chance of drug toxicity.

Dosage Regimen Considerations

In the previous chapter those factors that can influence the dosage of a drug were mentioned. The question of how much drug and how often to administer it for a desired therapeutic effect is not easily attainable. Basically, there are two approaches to

the development of dosage regimens. The first is the *empirical approach*, which involves the administration of a drug in a certain quantity, noting the therapeutic response and then modifying the dosage of drug and the dosing interval accordingly. Unfortunately, experience with the administration of a drug usually starts with the first patient, and eventually a sufficient number of patients receive the drug so that a fairly accurate prediction can be made. Besides the desired therapeutic effect, consideration must also involve the occurrence and severity of side effects. Empirical therapy is usually employed when the drug concentration in serum or plasma does not reflect the concentration of drug at the receptor site in the body, or the pharmacodynamic effect of the drug is not related (or correlated) with the receptor site drug concentration. Empirical therapy, for example, is utilized for many anticancer drugs that demonstrate effects long after they have been excreted from the body. It is difficult to relate the serum level of these drugs with the desired therapeutic effect.

The second approach to the development of a dosage regimen is through the use of pharmacokinetics or the *kinetic approach*. This approach is based on the assumption that the therapeutic and toxic effects of a drug are related to the amount of drug in the body or to the plasma (or serum) concentration of drug at the receptor site. Through careful pharmacokinetic evaluation of a drug's absorption, distribution, metabolism and excretion in the body from a single dose, the levels of drug attained from multiple dosing can be estimated. One can then determine the appropriateness of a dosage regimen to achieve a desired therapeutic concentration of drug in the body and evaluate the regimen based upon therapeutic response.

When one considers the development of a dosage regimen, pharmacokinetics is but one of a number of factors that should be considered. Table 4.11 illustrates a number of these. Certainly an important factor is the inherent activity, i.e., pharmacodynamics, and toxicity, i.e., toxicology of the drug. A second consideration is the pharmacokinetics of the drug, which are influenced by the dosage form in which the drug is administered to the patient, e.g., biopharmaceutical considerations. The third factor focuses upon the patient to whom the drug will be given and encompasses the clinical state of the patient and how the patient will be managed. Lastly, atypical factors may influence the dosage regimen. Collectively, all of these factors influence the dosage regimen.

Table 4.11. Factors That Determine a Dosage Regimen*

Activity-Toxicity			*Pharmacokinetics*
Minimum therapeutic dose			Absorption
Toxic dose			Distribution
Therapeutic index			Metabolism
Side effects			Excretion
Dose-response relationships			

<div align="center">Dosage Regimen</div>

Clinical Factors		*Other Factors*
Clinical State of Patient	*Management of Therapy*	
Age, weight, urine pH	Multiple drug therapy	Tolerance-dependence
Condition being treated	Convenience of regimen	Pharmacogenetics-idiosyncrasy
Existence of other disease states	Compliance of patient	Drug interactions

*Reprinted with permission from Rowland M, Tozer TN. Clinical Pharmacokinetics. 2nd Ed. Philadelphia: Lea & Febiger, 1989.

The dosage regimen of a drug may simply involve the administration of a drug once for its desired therapeutic effect, e.g., pinworm medication, or encompass the administration of drug for a specific time through multiple doses. In the latter instance, the objective of pharmacokinetic dosing is to design a dosage regimen that will continually maintain a drug's therapeutic serum or plasma concentration within the drug's therapeutic index, i.e., above the minimum effective concentration but below the minimum toxic level.

Frequently drugs are administered between 1 to 4 times per day, most often in a fixed dose, e.g., 75 mg 3 times daily after meals. As mentioned earlier, after a drug is administered its level within the body varies because of the influence of all of the processes, e.g., absorption, distribution, metabolism and excretion. A drug will accumulate in the body when the dosing interval is less than the time needed for the body to eliminate a single dose. For example, Figure 4.18 illustrates the plasma concentration for a drug given by intravenous administration and oral administration. The 50 mg dose of this drug was given at a dosing interval of 8 hours. The drug has an elimination half-life of 12 hours. As one can see with continued dosing the drug concentration reaches a *steady state* or *plateau* concentration. At this limit the amount of drug lost per interval is replenished when the drug is dosed again. Consequently the concentration of drug in the plasma or serum fluctuates between a minimum concentration and a maximum concentration. Thus for certain patient types it is optimal to target dosing so that the plateau concentration resides within the therapeutic index of a drug to maintain a minimum effective concentration of drug. For example, the asthmatic patient maintained on theophylline must have a serum concentration between 10 and 20 μg/mL. Otherwise the patient may be susceptible to an asthma attack. Thus, when dosing the asthmatic patient it is preferable to give theophylline around the clock 4 times daily to sustain levels at least above the minimum effective concentration. If on the other hand this medicine is only administered every 4 hours during the waking hours, it is possible that the minimum concentration will fall below effective levels between the at-bedtime dose and the next morning dose. Consequently, the patient may awaken in the middle of the night and exhibit an asthma attack.

Patients can be monitored pharmacokinetically through appropriate plasma, serum or blood samples, and some hospital pharmacies have implemented pharmacokinetic dosing services. The intent is to maximize drug efficacy, minimize drug toxicity and keep health care costs at a minimum. Thus, for example, complications associated with overdose are controlled or drug interactions that are known to occur, e.g., smoking-theophylline, can be accommodated. In these services, for exam-
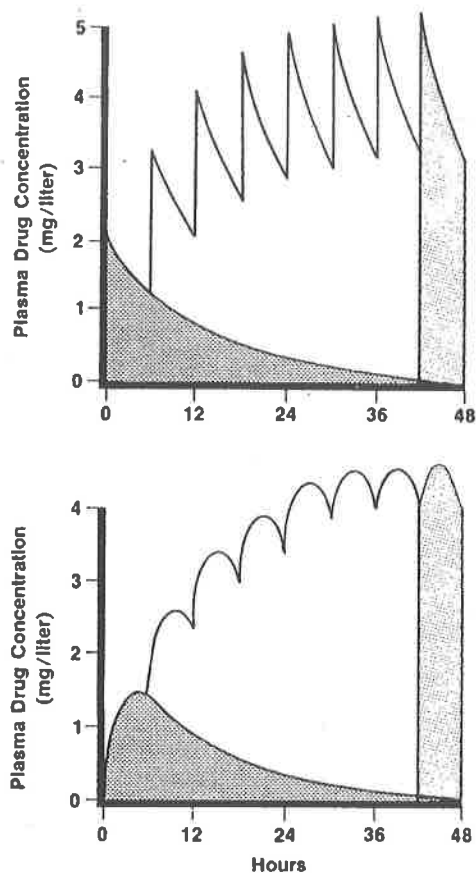
Fig. 4.18   *Plasma concentration of a drug given intravenously (top) and orally (bottom) on a fixed dose of 50 mg and fixed dosing interval of 8 hours. The half-life is 12 hours. Note that the area under the plasma concentration-time curve during a dosing interval at steady state is equal to the total area under the curve for a single dose. The fluctuation of the concentration is diminished when given orally (half-life of absorption is 1.4 hours) but the average steady-state concentration is the same as that after intravenous administration, since $F = 1$. (Reprinted with permission from Rowland M, Tozer TN. Clinical Pharmacokinetics. Philadelphia: Lea & Febiger, 1989).*

ple, once the physician prescribes a certain amount of drug and monitors the clinical response, it is the pharmacist who coordinates the appropriate sample time to determine drug concentration in the appropriate body fluid. After the level of drug is attained, it is the pharmacist who interprets the result, and consults with the physician regarding subsequent dosages.
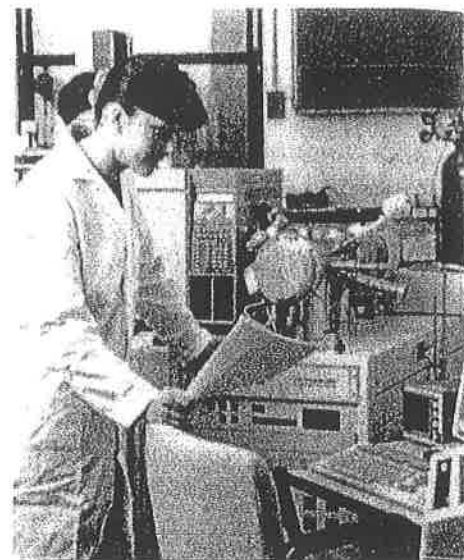

Fig. 4.19   *Computerized gas chromatography mass spectrometry used in bioanalytical studies. Consists of Hewlett Packard Gas Chromatograph (Model 5890 A) and VG Mass Spectrometer (Model UG 12–250). (Courtesy of Elan Corporation, plc.)*
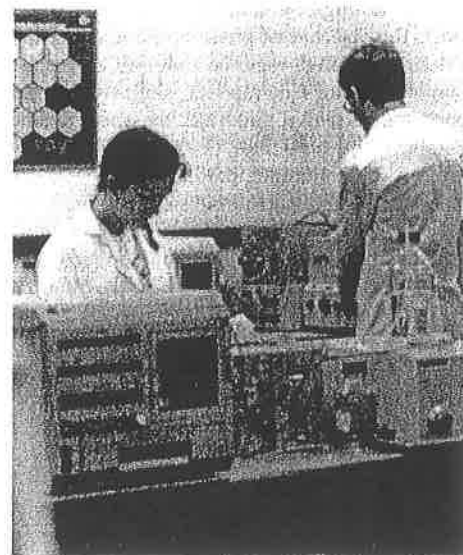

Fig. 4.20   *Assay of biological fluids using Waters HPLC (High Performance Liquid Chromatography) system consisting of (from left to right) Autosampler (Model 712 Wisp), Pump (Model M-45), Shimadzu Fluorescence Detector (Model RF-535). (Courtesy of Elan Corporation, plc.)*

Pharmacokinetic research has demonstrated that the determination of a patient's dosage regimen depends on numerous factors and daily dose formulas exist for a number of drugs that must be administered on a routine maintenance schedule, e.g., digoxin, procainamide, theophylline. For certain drugs such as digoxin, which are not highly lipid soluble, it is preferable to use a patient's lean body weight (LBW) rather than total body weight (TBW) to provide a better estimate of the patient's volume of distribution. Alternatively, even though pharmacokinetic dosing formulas may exist, one must be cognizant that patient factors may be more relevant. For example, with the geriatric patient it is advisable to begin drug therapy with the lowest possible dose and increase the dosage as necessary in small increments to optimize the patient's clinical response. Then the patient should be monitored for drug efficacy and reevaluated periodically. Examples of bioanalytical research laboratories are shown in Figures 4.19 and 4.20.

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