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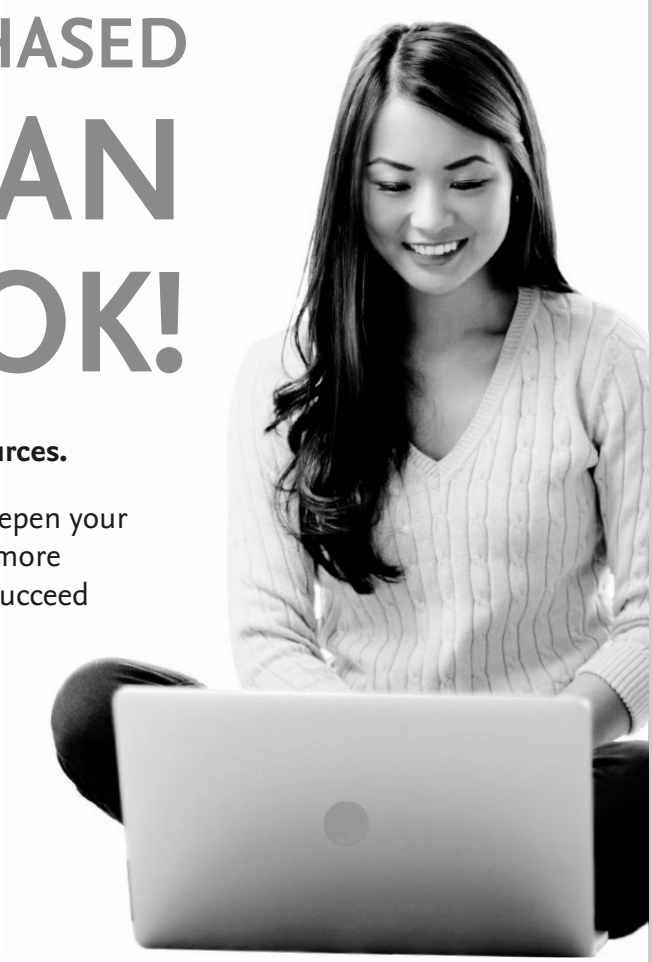

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Rau's Respiratory Care Pharmacology

TENTH EDITION

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To ALL respiratory therapists that dedicate themselves to improving the lives of patients and those around them.

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Preface

Rau's Respiratory Care Pharmacology, 10th edition, provides the most exhaustive and up-to-date information pertaining to the field of respiratory care pharmacology. The importance of this text stems from the ever-changing nature of the field. The improvement of existing drugs and the creation of new drugs that use the direct access that the lungs provide to the human body have expanded the types of drugs respiratory therapists are using today and will use in the future. This book provides the respiratory therapy student with a strong foundation of the drugs presently used in respiratory care. It also serves as a valuable resource for the respiratory care practitioner.

Organization

The text is organized into three specific, fully referenced, and comprehensive sections to allow the reader easy access to a particular section of interest. Unit One covers the basics of respiratory care pharmacology, including the principles of drug action, the basic methods of drug administration, the standard drug calculations, and the effects of drugs on body systems. Unit Two covers the drugs most frequently delivered to patients by respiratory therapists, and Unit Three covers the drugs used to treat critical care and cardiovascular patients, featuring an entirely new chapter on the role of the respiratory therapist in the emerging area of sleep and sleep pharmacology.

Distinctive Features

- For more than 30 years, *Rau's Respiratory Care Pharmacology* has been the preeminent respiratory care pharmacology text. In their passion for excellent patient care in the field of respiratory care, Dr. Gardenhire and his team of notable contributors are committed to engaging the reader.
- The up-to-date material reflects changes in the field and prepares students for careers as respiratory therapists in today's health care environment.
- Comprehensive coverage provides the most thorough explanations of any respiratory care pharmacology text on the market.
- Pharmacokinetic principles are discussed as they relate to respiratory agents, drug administration, and a range of specific drugs used in respiratory care and their effects on body systems.
- Consistent organization throughout and helpful learning tools give students the optimal opportunity for knowledge and growth.
- A thoroughly revised Student Workbook provides extra opportunities for review and self-assessment.

New to this Edition

- Continued improvement in readability provides greater comprehension of this complex material.
- The addition of clinical connections to assist the reader in the application of the agent in the clinical setting.
- Expansion of Evolve Learning Resources for respiratory therapy students includes electronic flashcards to assist study efforts and an NBRC Correlation Guide.
- Two appendices include a conversion chart for units and systems of measurement from customary U.S. imperial measures to the metric system as well as a list of the most commonly prescribed respiratory medications and acceptable mixtures.
- New drug cards have been created to provide detailed information on agents in a simple accessible form.

Pedagogic Features

- A consistent approach within each chapter begins with Chapter Outlines, measurable Objectives, and Key Terms with definitions identifying key information. Key pharmacologic agents are covered, noting the dosage and administration, mode of action, pharmacokinetics, and hazards and side effects. Each chapter ends with a series of Self-Assessment Questions and a Clinical Scenario to help readers assess their comprehension of the material. Answers are provided in Appendix A at the back of the book.
- Learning Objectives that parallel the levels tested by the National Board for Respiratory Care (NBRC) examinations help identify important information that goes beyond memorization and recall.
- Key Terms with definitions provide easy access to the pharmacologic vocabulary the respiratory therapy student should embrace.
- Full-color illustrations throughout highlight special features and draw out relevant details.
- Key Points boxes, located throughout each chapter, highlight concepts with which the reader should become familiar while working through the material.

Ancillaries

For the Instructor

For the 10th edition, the Evolve Resources for *Rau's Respiratory Care Pharmacology* provide an interactive learning environment designed to work in coordination with the textbook. It features a test bank, PPTs, case studies, an image collection, and an NBRC Correlation Guide.

The Test Bank includes more than 600 questions. There are more than 500 PowerPoint slides that include embedded animations and Automated Response System questions. Evolve may be used to publish the class syllabus, outlines, and lecture notes; set up "virtual office hours" and e-mail communication; share important

dates and information through the online class calendar; and encourage student participation through chat rooms and discussion boards. Evolve allows instructors to post examinations and manage their grade books online. For more information, visit http://evolve.elsevier.com/Gardenhire/Rau/respiratory/ or contact an Elsevier sales representative.

For the Student

The *Workbook for Rau's Respiratory Care Pharmacology* has been completely rewritten to provide a variety of exercises for each of the 23 chapters in the book. The ninth edition was reviewed and extensively revised to correspond with the learning objectives. All answers are referenced back to the text for ease in further review. Examples include NBRC-type questions, critical thinking exercises, case studies, definitions, and appropriate content review to help break down the difficult concepts in the textbook. The workbook creates a more complete learning package for students and allows the student exposure to more questions in addition to what is available in the text. The answers for the exercises are located on the Evolve Resources. Ask your instructor for details.

The Evolve Student Resources include electronic flashcards to assist study efforts and an NBRC Correlation Guide.

The continuing developments in respiratory drugs and in related critical care drug groups, with the increasing complexity and scope of material, challenge practitioners, students, and authors alike. Every effort has been made to ensure the accuracy of information on drugs in this text. However, practitioners are urged to review the manufacturer's detailed literature when administering a drug and to keep themselves informed of new developments in drug therapy.

Acknowledgments

The 10th edition of *Rau's Respiratory Care Pharmacology* is dedicated to all faculty members, students, and practitioners looking to share, begin, or maintain their knowledge in respiratory therapy. As with previous editions, this edition benefits from the substantial contributions of individuals who are experts in various areas of pharmacology and aerosol medicine. Their names and affiliations, too numerous to list here, are found in the list of Contributors. They have graciously provided invaluable material for this revised edition of the text. I thank all of them for their wisdom and kindness in preparing their chapters.

I want to thank all faculty, staff, and students of the Department of Respiratory Therapy at Georgia State University. Each of you is meaningful to me in both my personal life and my professional life. It is you who make the department a place that I look forward to coming to each morning. I could not do most of what I do or have done without your assistance!

Thank you to my former student Sandra T. Hinski, PhD, RRT, RRT-NPS, Program Director at Gateway Community College in Phoenix, Arizona, for her dedication and for writing the workbook and ancillary material. The Hinski way is the only way and is working beautifully!

I am grateful to the reviewers who provided me direction and clarification based on their experiences in the classroom and the hospital. I also appreciate the efforts of all those who worked so tirelessly behind the scene to make sure that this book made it to market. A huge thank you to Yvonne Alexopoulous for her oversight and her ability get the project stated. I want to acknowledge Heather Bays for her assistance in starting the project and agreeing to take my early morning calls! Finally, I would like to express my gratitude to Melissa Rawe for her ability to pick up the project and get it to the finish line.

Thank you to my wife, Robin, and my girls, Ali and Ella, for warming my heart. I am always attempting to do better for each of you!

Finally I must recognize all of the students and therapists who have and will continue to learn from this textbook. Thank you for allowing me to be a small part of your career!

Douglas S. Gardenhire, EdD, RRT, RRT-NPS, FAARC

"If a man is called to be a street sweeper, he should sweep streets even as Michelangelo painted or Beethoven composed music or Shakespeare wrote poetry. He should sweep streets so well that all the hosts of heaven and earth will pause to say, 'Here lived a great street sweeper who did his job well.' "

Martin Luther King, Jr.

Contents

UNIT **A**

Basic Concepts and Principles in Pharmacology

1

Introduction to Respiratory Care Pharmacology

DOUGLAS S. GARDENHIRE

CHAPTER OUTLINE

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define pharmacology
2. Define drugs
3. Describe how drugs are named
4. List the various sources of drug information
5. List the various sources used to manufacture drugs
6. Describe the process for drug approval in the United States
7. Define orphan drugs
8. Differentiate between prescription drugs and over-the-counter (OTC) drugs
9. Apply the various abbreviations and symbols used in prescribing drugs
10. Describe the therapeutic purpose of each of the major aerosolized drug groups
11. Identify related drug groups in respiratory care

KEY TERMS AND DEFINITIONS

Acute respiratory distress syndrome (ARDS) Respiratory disorder characterized by respiratory insufficiency that may occur as a result of trauma, pneumonia, oxygen toxicity, gram-negative sepsis, and systemic inflammatory response.

Aerosolized agents Group of aerosol drugs for pulmonary applications that includes adrenergic, anticholinergic, mucoactive, corticosteroid, antiasthmatic, and antiinfective agents and surfactants instilled directly into the trachea.

Airway resistance *(R_{aw})* Measure of the impedance to ventilation caused by the movement of gas through the airway.

Brand name See Trade name.

Chemical name Name indicating the chemical structure of a drug.

Chronic obstructive pulmonary disease (COPD) Disease process characterized by airflow limitation that is not fully reversible, is usually progressive, and is associated with an abnormal inflammatory response of the lung to noxious particles or gases. Diseases that cause airflow limitation include chronic bronchitis, emphysema, asthma, and bronchiectasis.

Code name Name assigned by a manufacturer to an experimental chemical that shows potential as a drug. An example is aerosol SCH 1000, which was the code name for ipratropium bromide, a parasympatholytic bronchodilator (see Chapter 7).

Cystic fibrosis (CF) Inherited disease of the exocrine glands, affecting the pancreas, respiratory system, and apocrine glands. Symptoms usually begin in infancy and are

characterized by increased electrolytes in sweat, chronic respiratory infection, and pancreatic insufficiency.

Drug administration Method by which a drug is made available to the body.

Generic name Name assigned to a chemical by the United States Adopted Name (USAN) Council when the chemical appears to have therapeutic use and the manufacturer wishes to market the drug.

Nonproprietary name Name of a drug other than its trademarked name.

Official name In the event that an experimental drug becomes fully approved for general use and is admitted to the *United States Pharmacopeia–National Formulary (USP-NF),* the generic name becomes the official name.

Orphan drug Drug or biologic product for the diagnosis or treatment of a rare disease (affecting fewer than 200,000 persons in the United States).

Pharmacodynamics Mechanisms of drug action by which a drug molecule causes its effect in the body.

Pharmacogenetics Study of the interrelationship of genetic differences and drug effects.

Pharmacognosy Identification of sources of drugs, from plants and animals.

Pharmacokinetics Time course and disposition of a drug in the body, based on its absorption, distribution, metabolism, and elimination.

Pharmacology Study of drugs (chemicals), including their origins, properties, and interactions with living organisms.

Pharmacy Preparation and dispensing of drugs.

***Pneumocystis jiroveci* (formerly *carinii*)** Organism causing *Pneumocystis* pneumonia in humans, seen in immunosuppressed individuals, such as those infected with human immunodeficiency virus (HIV).

Prescription Written order for a drug, along with any specific instructions for compounding, dispensing, and taking the drug. This order may be written by a physician, osteopath, dentist, veterinarian, and others but not by chiropractors or opticians.

Pseudomonas aeruginosa A gram-negative organism, primarily a nosocomial pathogen. It causes urinary tract infections, respiratory system infections, dermatitis, soft tissue infections, bacteremia, bone and joint infections, gastrointestinal infections, and various systemic infections, particularly in patients with severe burns and in patients who are immunosuppressed (e.g., patients with cancer or acquired immunodeficiency syndrome [AIDS]).

Respiratory care pharmacology Application of pharmacology to the treatment of pulmonary disorders and, more broadly, critical care. This chapter introduces and defines basic concepts and selected background information useful in the pharmacologic treatment of respiratory disease and critical care patients.

Respiratory syncytial virus (RSV) Virus that causes the formation of syncytial masses in cells. This leads to inflammation of the bronchioles, which may cause respiratory distress in young infants.

Therapeutics Art of treating disease with drugs.

Toxicology Study of toxic substances and their pharmacologic actions, including antidotes and poison control.

Trade name Brand name, or proprietary name, given to a drug by a particular manufacturer.

Pharmacology and the Study of Drugs

KEY POINT

Key terms in the study of pharmacology are introduced, including *drug* and *pharmacology.* The study of **respiratory care pharmacology** is broadly defined as the application of pharmacology to cardiopulmonary disease and critical care.

The many complex functions of the human organism are regulated by chemical agents. Chemicals interact with an organism to alter its function, providing methods of diagnosis, treatment, or prevention of disease. Such chemicals are termed *drugs.* A drug is any chemical that alters the organism's functions or processes. Examples include oxygen, alcohol, lysergic acid diethylamide (LSD), heparin, epinephrine, and vitamins. The study of drugs (chemicals), including their origins, properties, and interactions with living organisms, is the subject of **pharmacology**.

Pharmacology can be subdivided into the following more specialized topics:

Pharmacy: The preparation and dispensing of drugs
Pharmacognosy: The identification of sources of drugs, from plants and animals
Pharmacogenetics: The study of the interrelationship of genetic differences and drug effects
Therapeutics: The art of treating disease with drugs
Toxicology: The study of toxic substances and their pharmacologic actions, including antidotes and poison control

The principles of drug action from dose administration to effect and clearance from the body are the subject of processes known as **drug administration**, **pharmacokinetics**, and **pharmacodynamics**. These processes are defined and presented in detail in Chapter 2. Table 1.1 summarizes key developments in the regulation of drugs in the United States.

Naming Drugs

KEY POINT

Each drug has five different names: chemical, code, official, generic, and trade (or brand). Sources of drug information include references, such as the *Physicians' Desk Reference (PDR)* and the *United States Pharmacopeia–National Formulary (USP-NF);* textbooks, such as Goodman & Gilman's *The Pharmacological Basis of Therapeutics;* and subscription services, such as *Drug Facts and Comparisons* and *Clinical Pharmacology* by Gold Standard.

TABLE 1.1 Legislation Affecting Drugs

1906	First *Food and Drugs Act* is passed by Congress; the *USP* and the *NF* were given official status.
1914	*Harrison Narcotic Act* is passed to control the importation, sale, and distribution of opium and its derivatives as well as other narcotic analgesics.
1938	*Food, Drug, and Cosmetic Act* becomes law. This is the current federal *Food, Drug, and Cosmetic Act* to protect the public health and to protect physicians from irresponsible drug manufacturers. This act is enforced by the FDA.
1952	*Durham-Humphrey Amendment* defines the drugs that may be sold by the pharmacist only on prescription.
1962	*Kefauver-Harris Amendment* is passed as an amendment to the *Food, Drug, and Cosmetic Act* of 1938. This law requires proof of the safety and efficacy of all drugs introduced since 1938. Drugs in use before that time have not been reviewed but are under study.
1970	*Controlled Substances Act* becomes effective; this act lists requirements for the control, sale, and dispensation of narcotics and dangerous drugs. Five schedules of controlled substances have been defined. Schedule I to Schedule V generally define drugs of decreasing potential for abuse, increasing medical use, and decreasing physical dependence. Examples of each schedule are as follows:
Schedule I	All nonresearch use is illegal; examples—heroin, marijuana, LSD, peyote, and mescaline.
Schedule II	No telephone prescriptions, no refills; examples—opium, morphine, certain barbiturates, amphetamines.
Schedule III	Prescription must be rewritten after 6 months or five refills; examples—certain opioid doses, anabolic steroids, and some barbiturates.
Schedule IV	Prescription must be rewritten after 6 months or five refills; penalties for illegal possession differ from those for Schedule III drugs; examples—phenobarbital, barbital, chloral hydrate, meprobamate (Equanil, Miltown), and zolpidem (Ambien).
Schedule V	As for any nonopioid prescription drug; examples—narcotics containing nonnarcotics in mixture form, such as cough preparations or Lomotil (diphenoxylate [narcotic; 2.5 mg] and atropine sulfate [nonnarcotic]).
1972	*Drug Listing Act* requires drug establishments that are engaged in the manufacturing, preparation, propagation, processing, or compounding of a drug to register their establishments and list all of their commercially marketed drug products with the FDA. This requirement includes establishments that repackage or change the container, labeling, or wrapper of any drug package in the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the customer.
1983	*Orphan Drug amendments* provided incentives for the development of drugs that treat diseases that affect fewer than 200,000 patients in the United States.
1984	*Drug Price Competition and Patent Restoration Act* provided abbreviated new drug application for generic medication. Allowed the patent to be extended for up to 5 years as a result of loss of marketing because of FDA reviews.
1992	*Prescription Drug User Fee Act* was reauthorized in 2007. User fees are paid for certain new drug applications by manufacturers.
1994	*Dietary Supplement Health and Education Act* established standards of dietary supplements. Specific ingredient and nutrition labels must be included on each package.
2002	*Bioterrorism Act* provided more stringent control on biologic agents and toxins.
2007	*FDA Amendments Act* gave the FDA greater authority over drug labeling, marketing, and advertising. Made clinical trial information more visible to the public.
2012	*FDA Safety and Innovation Act (FDASIA)* provided the FDA with power to collect fees (reauthorization from 2007), expedite agents of clinical significance, learn from patients first hand, and protect the global drug supply chain. All are efforts to make medications safer for U.S. citizens.

For more information, access the FDA website at www.fda.gov.
FDA, Food and Drug Administration; *LSD,* lysergic acid diethylamide; *NF, National Formulary; USP, United States Pharmacopeia.*

A manufacturer of a drug or pharmacologic agent must complete numerous steps set forth by the U.S. Food and Drug Administration (FDA). Along the way, each agent picks up various labels rather than having a single name. An agent that becomes officially approved for general clinical use in the United States will have accumulated at least five different names, as follows:

Chemical name: The name indicating the drug's chemical structure.

Code name: A name assigned by a manufacturer to an experimental chemical that shows potential as a drug. An example is aerosol SCH 1000, which was the code name for ipratropium bromide, a parasympatholytic bronchodilator (see Chapter 7).

Generic name: The name assigned to a chemical by the United States Adopted Name (USAN) Council when the chemical appears to have therapeutic use and the manufacturer wishes to market the drug. Instead of a numeric or alphanumeric code, as in the code name, this name often is loosely based on the drug's chemical structure. For example, isoproterenol has an isopropyl group attached to the terminal nitrogen on the amino side chain, whereas metaproterenol is the same chemical structure as isoproterenol except that a dihydroxy attachment on the catechol nucleus is now in the so-called meta position (carbon-3,5 instead of carbon-3,4). The generic name is also known as the **nonproprietary name**, in contrast to the brand name.

Official name: In the event that an experimental drug becomes fully approved for general use and is admitted to the *USP-NF,* the generic name becomes the official name. Because an officially approved drug may be marketed by many manufacturers under different names, it is recommended that clinicians use the official name, which is nonproprietary, and not brand names.

Trade name: This is the **brand name**, or proprietary name, given by a particular manufacturer. For example, the generic drug named albuterol is currently marketed by Schering-Plough as Proventil-HFA, by GlaxoSmithKline as Ventolin-HFA, and by Teva as Proair HFA.

Following is an example of the various names for the drug zafirlukast, an agent intended to control asthma:

Chemical name: 4-(5-cyclopentyloxy-carbonylamino-1-methyl-indol-3-ylmethyl)-3-methoxy-*N*-o-tolylsulfonylbenz-amide
Code name: ICI 204,219
Generic name: zafirlukast
Official name: zafirlukast
Trade (or brand) name: Accolate (AstraZeneca)

Sources of Drug Information

The *USP-NF* is a book of standards containing information about medications, dietary supplements, and medical devices. The FDA considers this book the official standard for drugs marketed in the United States.

Another source of drug information is the *Physicians' Desk Reference (PDR).* Although prepared by manufacturers of drugs and potentially lacking the objectivity of the *USP-NF,* this annual volume provides useful information, including descriptive color charts for drug identification, names of manufacturers, and general drug actions.

The Drug Listing Act of 1972 requires registered drug establishments to provide the FDA with a current list of all drugs manufactured, propagated, prepared, processed, or compounded for commercial distribution. Drug products are identified and reported by using a unique, three-segment number, called the National Drug Code (NDC), which serves as a product identifier for drugs. If searching for specific product information on drugs used in the United States you may search the NDC database at http://www.accessdata.fda.gov/scripts/cder/ndc/.

A comprehensive and in-depth discussion of general pharmacologic principles and drug classes can be found in several texts. Two examples are the following (see References for a complete listing):

- Goodman & Gilman's *The Pharmacological Basis of Therapeutics,* ed. 12[1]
- *Basic and Clinical Pharmacology,* ed. 14[2]

An excellent way to obtain information on drug products and new releases is the monthly subscription service provided as *Drug Facts and Comparisons,* published by Facts & Comparisons.[3]

Sources of Drugs

Although the source of drugs is not a crucial area of expertise for the respiratory care clinician, it can be extremely interesting. Recognition of naturally occurring drugs dates back to Egyptian papyrus records, to the ancient Chinese, and to the early Central American civilizations and is still recognized in remote regions of modern America, such as Appalachia.

For example, the prototype of cromolyn sodium was khellin, found in the eastern Mediterranean plant *Ammi visnaga;* this plant was used in ancient times as a muscle relaxant. Today, its synthetic derivative is used as an antiasthmatic agent. Another example is curare, derived from *Chondrodendron tomentosum* (a large vine) and used by South American Indians to coat their arrow tips for lethal effect. Its derivative is now used as a neuromuscular blocking agent. Digitalis is obtained from the foxglove plant *(Digitalis purpurea)* and was reputedly used by the Mayans for relief of angina. This cardiac glycoside is now used to treat heart conditions. The notorious poppy seed *(Papaver somniferum)* is the source of the opium alkaloids, immortalized in the book *Confessions of an English Opium-Eater.*[4]

Today, the most common source of drug preparation is chemical synthesis. Plants, minerals, and animals have often contributed to the synthesis of drug preparation. Examples of these sources include the following:

- *Animal:* thyroid hormone, insulin, pancreatic dornase
- *Plant:* Khellin *(Ammi visnaga);* atropine (belladonna alkaloid); digitalis (foxglove); reserpine *(Rauwolfia serpentina);* volatile oils of eucalyptus, pine, anise
- *Mineral:* copper sulfate, magnesium sulfate (Epsom salts), mineral oil (liquid hydrocarbons)

Process for Drug Approval in the United States

KEY POINT

The process of drug approval in the United States is lengthy and expensive and involves multiple phases.

The process by which a chemical moves from the status of a promising potential drug to one fully approved by the FDA for general clinical use is, on average, long, costly, and complex. Cost estimates vary, but in the 1980s, it took an average of 13 to 15 years from chemical synthesis to marketing approval by the FDA, with a cost of $350 million in the United States.[5] In a study done in 2003 by DiMasi et al.,[6] it was calculated that companies spend over $800 million on research and development and on preclinical and postclinical trials of a new drug. Adams and Brantner[7] replicated DiMasi's calculations and estimated that companies spent over $1 billion in 2010 to bring a new drug to market. DiMasi et al.[8] have found that, today, pharmaceutical companies spend, on average, $2.6 billion per drug to release a drug into the U.S. market.

The major steps in the drug approval process have been reviewed by Flieger[9] and by Hassall and Fredd.[10] Box 1.1 outlines the major steps of the process.

Chemical Isolation and Identification

Because a drug is a chemical, the first step in drug development is to identify a chemical with the potential for useful physiologic effects. This step is exemplified by the plant product paclitaxel, which is derived from the needles and bark of the western yew tree *(Taxus brevifolia).* Paclitaxel showed antitumor activity, making it attractive for investigation as an anticancer drug. As the first step in the process of drug approval, the exact structure and physical

• BOX 1.1 Major Steps in the Process of Marketing a Drug in the United States

Isolation and Identification of the Chemical
Animal studies
General effects
Special effects on organ systems
Toxicology studies

Investigational New Drug (IND) Approval
Phase 1 studies: Small number, healthy subjects
Phase 2 studies: Small number, subjects with disease
Phase 3 studies: Large, multicenter studies

New Drug Application (NDA)
Reporting system for first 6 months

• BOX 1.2 Alphanumeric Coding System of the FDA

Chemical/Pharmaceutical Standing
1 = New chemical entity
2 = New salt form
3 = New dosage form
4 = New combination
5 = Generic drug
6 = New indication

Therapeutic Potential
A = Important (significant) therapeutic gain over other drugs
AA = Important therapeutic gain, indicated for a patient with AIDS; fast-track
B = Modest therapeutic gain
C = Important options; little or no therapeutic gain

AIDS, *Acquired immunodeficiency syndrome;* FDA, *U.S. Food and Drug Administration.*

and chemical characteristics of paclitaxel were established. Paclitaxel was subsequently developed and marketed as Taxol by Bristol-Myers Squibb.

Animal Studies

Once an active chemical is isolated and identified, a series of animal studies is performed to examine its general effect on the animal and effects on specific organs, such as the liver or kidneys. Toxicology studies to examine mutagenicity, teratogenicity, effect on reproductive fertility, and carcinogenicity are also performed.

Investigational New Drug Approval

At this point, an Investigational New Drug (IND) application is filed with the FDA for the chemical being examined. The IND application includes all of the information previously gathered, as well as plans for human studies. These studies proceed in three phases and usually require about 3 years to complete.

Phase 1

The drug is investigated in a small group of healthy volunteers to establish its activity. This investigation is the basis for the pharmacokinetic description of the drug (rates of absorption, distribution, metabolism, and elimination).

Phase 2

The drug is then investigated as a treatment in a small number of individuals with the disease the drug is intended to treat.

Phase 3

The drug is investigated in large, multicenter studies to establish safety and efficacy.

New Drug Application

After a successful IND process, a New Drug Application (NDA) is filed with the FDA, and on approval, the drug is released for general clinical use. A detailed reporting system is in place for the first 6 months to track any problems that arise with the drug's use. The drug is no longer considered experimental (investigational) and can be prescribed for treatment of the general population by physicians.

The involved, lengthy, and expensive process of obtaining approval from the FDA to market a new drug in the United States has often been criticized.

FDA New Drug Classification System

Because some drugs are simply released in new forms or are similar to previously approved agents, the FDA has a classification system to help identify the significance of new products.[11] An alphanumeric code is given to provide this information (Box 1.2).

Orphan Drugs

KEY POINT

Certain drugs used for rare diseases, which may not return the cost of their development, are termed *orphan drugs.*

An **orphan drug** is a drug or biologic product used for the diagnosis or treatment of a rare disease. *Rare* is defined as a disease that affects fewer than 200,000 persons in the United States. Alternatively, a drug may be designated as an orphan if it is used for a disease that affects more than 200,000 persons but there is no reasonable expectation of recovering the cost of drug development. Table 1.2 lists several orphan drugs of interest to respiratory care clinicians.

The Prescription

KEY POINT

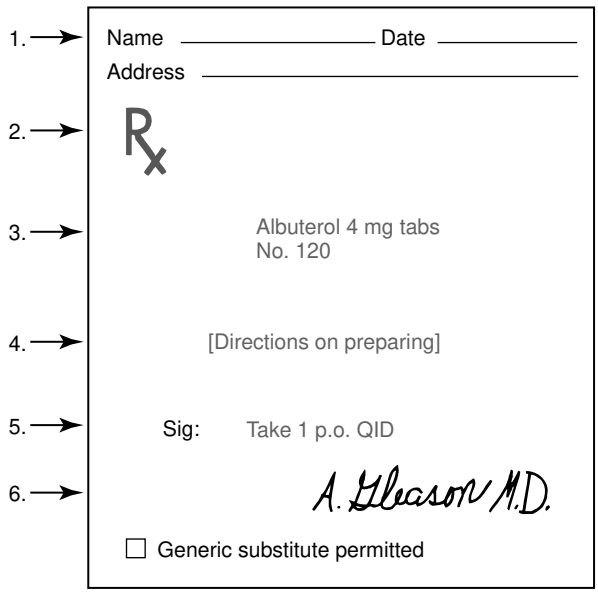
The selling of many drugs requires a health care prescriber's order, known as the *prescription,* and may involve Latin terms and abbreviations.

The **prescription** is the written order for a drug, along with any specific instructions for compounding, dispensing, and taking the drug. This order may be written by a physician, osteopath, dentist, veterinarian, and other health care practitioners, such as a physician assistant and nurse practitioner, but not by chiropractors or opticians. Today, although many prescriptions are written and distributed by electronic means, it is important to note that written prescriptions

TABLE 1.2 Examples of Orphan Drugs of Interest to Respiratory Care Clinicians

Drug	Proposed Use
Acetylcysteine	Intravenous administration for moderate to severe acetaminophen overdose
α_1-Proteinase inhibitor (Prolastin)*	Replacement therapy for congenital α_1-proteinase (α_1-antitrypsin) deficiency
Beractant (Survanta)*	Prevention or treatment of RDS in newborns
CF transmembrane conductance regulator	Treatment of CF
Dornase alfa (Pulmozyme)*	Treatment of CF: reduction of mucus viscosity and increase in airway secretion clearance
Nitric oxide gas (INOmax)*	Treatment of persistent pulmonary hypertension of newborns or of ARDS in adults
Tobramycin solution for inhalation (TOBI)*	Treatment of *Pseudomonas aeruginosa* in CF or bronchiectasis
Pentamidine isethionate	Prevent *Pneumocystis jiroveci* (formerly *carinii*) pneumonia in high-risk patients

*Use has been approved by the FDA.
ARDS, Acute respiratory distress syndrome; *CF,* cystic fibrosis; *RDS,* respiratory distress syndrome.



• **Fig. 1.1** Parts of a prescription. 1. Patient's name and address and the date the prescription was written. 2. ℞ (meaning "recipe" or "take thou") directs the pharmacist to take the drug listed and prepare the medication. This is referred to as the *superscription.* 3. The inscription lists the name and quantity of the drug being prescribed. 4. When applicable, the health care prescriber includes a subscription, which provides directions to the pharmacist on how to prepare the medication. For example, a direction to make an ointment, which might be appropriate for certain medications, would be "ft ung." In many cases, with precompounded drugs, counting out the correct number is the only requirement. 5. *Sig (signa)* means "write." The transcription or signature is the information the pharmacist writes on the label of the medication as instructions to the patient. 6. Name of the prescriber: Although the health care prescriber signs the prescription, the word "signature," as described in Part 5, denotes the directions to the patient, not the prescriber's name.

are still used. The detailed parts of a prescription are shown in Fig. 1.1. It should be noted that Latin and English, as well as metric and apothecary measures, are used for drug orders.

The directions (see *4* in Fig. 1.1) to the pharmacist for mixing or compounding drugs have become less necessary with the advent of the large pharmaceutical firms and their prepared drug products. The importance of these directions is in no way diminished, however, because misinterpretation is potentially lethal when dealing with drugs.

Since passage of the Controlled Substances Act of 1971, health care practitioners must include their registration number provided by the Drug Enforcement Administration (DEA) (usually termed a *DEA registration number*) when prescribing narcotics or controlled substances. Any licensed health care practitioner that has prescription rights may apply for a DEA registration number.

Table 1.3 lists the most common abbreviations seen in prescriptions.

Over-the-Counter Drugs

KEY POINT

An over-the-counter (OTC) drug does not require a prescription for purchase.

Many drugs are available to the general population without a prescription; these are referred to as *over-the-counter (OTC)* products. Although the strength and amount per dose may be less than that of a prescription formulation, OTC drugs can be hazardous, even in normal amounts, if their effects are not understood. In addition, when taken in large quantities, OTC products may increase risks to the consumer.

CLINICAL CONNECTION

For patients with mild asthma, racemic epinephrine is available over the counter (OTC) as an inhalation solution named Asthmanefrin. Racemic epinephrine can provoke cardiac arrhythmia or hypertension and, in particular, can exacerbate these conditions if they preexist in a patient. Dependence on OTC preparations may encourage "self-treatment" that could mask or complicate a serious medical condition.

Generic Substitution in Prescriptions

A health care prescriber can indicate to the pharmacist that generic substitution is permitted in the filling of a prescription. In such a case, the pharmacist may provide any manufacturer's version of the prescribed drug and not a specific brand. This practice is intended to save money because the manufacturer of the generic substitute has not invested considerable time and money in developing the original drug product, and presumably the generic substitute is less expensive to the consumer compared with the original proprietary brand.

TABLE 1.3 Abbreviations and Symbols Used in Prescriptions*

Abbreviation	Meaning	Abbreviation	Meaning
ā	before	ol	oil
āā	of each	OS	left eye
ac	before a meal	OU	both eyes
ad lib	as much as desired	p̄	after
alt hor	every other hour	part aeq	equal parts
aq dest	distilled water	pc	after meals
bid	twice daily	pil	pill
C, cong	gallon	placebo	I please (inert substitute)
c̄	with	po	per os (by mouth)
cap	capsule	prn	as needed
cc	cubic centimeter (another term for milliliter [mL])	pr	rectally
dil	dilute	pulv	powder
dtd	give such doses	q	every
elix	elixir	qh	every hour
emuls	emulsion	qid	four times daily
et	and	qod	every other day
ex aq	in water	qd	every day
ext	extract	q2h	every 2 hours
fld	fluid	q3h	every 3 hours
ft	make	q4h	every 4 hours
gel	a gel, jelly	qs	as much as required (quantity sufficient)
g	gram	qt	quart
gr	grain	Rx, ℞	take
gtt	a drop	s̄	without
hs	at bedtime	sig	write
IM	intramuscular	sol	solution
IV	intravenous	solv	dissolve
L	liter	sos	if needed (for one time)
lin	liniment	spt	spirit
liq	liquid, solution	sp frumenti	whiskey
lot	lotion	s̄s̄	half
M	mix	stat	immediately
mist, mixt	mixture	syr	syrup
mL	milliliter	tab	tablet or tablets
nebul	a spray	tid	three times daily
non rep	not to be repeated	tr, tinct	tincture
npo	nothing by mouth	ung	ointment
O, ō	pint	ut dict	as directed
OD	right eye	vin	wine

*Not all of these abbreviations are considered safe practice; however, they may still be seen occasionally.

Respiratory Care Pharmacology: an Overview

KEY POINT

Aerosolized agents are central to respiratory care in pulmonary diseases. This group of drugs includes adrenergic, anticholinergic, mucoactive, corticosteroid, antiasthmatic, and antiinfective agents and surfactants instilled directly into the trachea. Other drug groups important in respiratory care include cardiovascular, antiinfective, neuromuscular-blocking, and diuretic agents.

Helping people with pulmonary diseases, such as **cystic fibrosis (CF)**, or pulmonary derangements, such as **acute respiratory distress syndrome (ARDS)**, defines a spectrum of pharmacologic care from maintenance support of a person with stable disease through intervention for a critically ill patient. The respiratory system cannot be dissociated from the cardiac and vascular systems, given the interlinked function of these systems. As a result, respiratory care pharmacology involves a relatively broad area of drug classes.

Aerosolized Agents Given by Inhalation

Drugs delivered by oral inhalation or nasal inhalation are intended to provide a local topical treatment of the respiratory tract. The following are advantages of this method and route of delivery:

- Aerosol doses are smaller than doses used for the same purpose and given systemically.
- Side effects are usually fewer and less severe with aerosol delivery than with oral or parenteral delivery.
- The onset of action is rapid.
- Drug delivery is targeted to the respiratory system, with lower systemic bioavailability.
- The inhalation of aerosol drugs is painless, is relatively safe, and may be convenient, depending on the specific delivery device used.

The classes of aerosolized agents (including surfactants, which are directly instilled into the trachea), their uses, and individual agents are summarized in Table 1.4.

TABLE 1.4 Common Agents Used in Respiratory Therapy

Drug Group	Therapeutic Purpose	Agents
Adrenergic agents	*β-Adrenergic:* Relaxation of bronchial smooth muscle and bronchodilation, to reduce **airway resistance (R_{aw})** and to improve ventilatory flow rates in airway obstruction resulting from **chronic obstructive pulmonary disease (COPD)**, asthma, CF, acute bronchitis	Albuterol Arformoterol Formoterol Indacaterol Levalbuterol Metaproterenol Olodaterol Salmeterol Vilanterol
	α-Adrenergic: Topical vasoconstriction and decongestion Used to treat upper airway swelling	Racemic epinephrine
Anticholinergic agents	Relaxation of cholinergically induced bronchoconstriction to improve ventilatory flow rates in COPD and asthma	Aclidinium bromide Glycopyrrolate bromide Ipratropium bromide Tiotropium bromide Umeclidinium bromide
Mucoactive agents	Modification of properties of respiratory tract mucus; current agents reduce viscosity and promote clearance of secretions	Acetylcysteine Dornase alfa Hyperosmolar saline Mannitol
Corticosteroids	Reduction and control of airway inflammatory response usually associated with asthma (lower respiratory tract) or with seasonal or chronic rhinitis (upper respiratory tract)	Beclomethasone dipropionate Budesonide Ciclesonide Flunisolide Fluticasone furoate Fluticasone propionate Mometasone furoate
Antiasthmatic agents	Prevention of onset and development of the asthmatic response through inhibition of chemical mediators of inflammation	Cromolyn sodium Benralizumab Mepolizumab Montelukast Omalizumab Relizumab Zafirlukast Zileuton

Continued

TABLE 1.4 Common Agents Used in Respiratory Therapy—cont'd

Drug Group	Therapeutic Purpose	Agents
Antiinfective agents	Inhibition or eradication of specific infective agents, such as *Pneumocystis jiroveci (formerly carinii)* (pentamidine), respiratory syncytial virus (RSV) (ribavirin), *Pseudomonas aeruginosa* in CF or influenza A and B	Aztreonam Pentamidine Ribavirin Tobramycin Zanamivir
Exogenous surfactants	Approved clinical use is by direct intratracheal instillation for the purpose of restoring more normal lung compliance in RDS of newborns	Beractant Calfactant Lucinactant Poractant alfa
Prostacyclin analogs	Clinically indicated to treat pulmonary hypertension for the purpose of decreasing shortness of breath and increasing walking distance	Iloprost Treprostinil

CF, Cystic fibrosis; *RDS,* respiratory distress syndrome.

Related Drug Groups in Respiratory Care

Additional groups of drugs important in critical care are the following:

- *Antiinfective agents,* such as antibiotics or antituberculous drugs
- *Neuromuscular blocking agents,* such as curariform agents and others
- *Central nervous system agents,* such as analgesics and sedatives/hypnotics
- *Antiarrhythmic agents,* such as cardiac glycosides and lidocaine
- *Antihypertensive and antianginal agents,* such as β-blocking agents or nitroglycerin
- *Anticoagulant and thrombolytic agents,* such as heparin or streptokinase
- *Diuretics,* such as the thiazides or furosemide

SELF-ASSESSMENT QUESTIONS

Answers can be found in Appendix A.

1. What is the definition of the term *drug?*
2. What is the difference between the generic name and trade name of a drug?
3. What part of a prescription contains the name and amount of the drug being prescribed?
4. A physician's order reads as follows: "gtt iv of racemic epinephrine, c̄ 3 cc of normal saline, q4h, while awake." What has been ordered?
5. The drug salmeterol was released for general clinical use in the United States in 1994. Where would you look to find information about this drug, such as the available dosage forms, doses, properties, side effects, and action?

CLINICAL SCENARIO

Answers can be found in Appendix A.

A 24-year-old man played golf on a newly mown course. He had exhibited allergies in the past few years and was diagnosed as having asthma. He did not have a regular physician or medical treatment site, and he was not taking any medications to control his asthma and allergies. He began to experience difficulty breathing later in the day, with wheezing and some shortness of breath on mild exertion. He visited his local drugstore and purchased Primatene Mist. On use, he obtained immediate relief for his breathing, but his heart rate increased from 66 beats/min to 84 beats/min, and he felt shaky. By midnight, his wheezing had returned. He continued using the Primatene Mist through the next morning. The relief he experienced with use of the drug diminished during the afternoon, and a friend found him later that evening with audible wheezing, gasping for air, and in severe respiratory distress. The patient was rushed to a local emergency department, where he went into respiratory arrest approximately 5 minutes after arrival.

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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2
Principles of Drug Action

DOUGLAS S. GARDENHIRE

CHAPTER OUTLINE

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define key terms that pertain to principles of drug action
2. Define *drug administration phase*
3. Describe the various routes of administration available
4. Define *pharmacokinetic phase*
5. Discuss the key factors in the pharmacokinetic phase (e.g., absorption, distribution, metabolism, and elimination)
6. Describe the first-pass effect
7. Differentiate between systemic and inhaled drugs in relation to the pharmacokinetic phase
8. Explain the lung availability/total systemic availability (L/T) ratio
9. Define *pharmacodynamic phase*
10. Discuss the importance of structure–activity relationships
11. Discuss the role of drug receptors
12. Discuss the importance of dose–response relationships
13. Describe the importance of pharmacogenetics

KEY TERMS AND DEFINITIONS

Agonist Chemical or drug that binds to a receptor and creates an effect on the body.
Antagonist Chemical or drug that binds to a receptor but does not create an effect on the body; it blocks the receptor site from accepting an agonist.
Bioavailability Amount of drug that reaches the systemic circulation.
Drug administration Method by which a drug is made available to the body.
Enteral Use of the intestine.
First-pass effect Initial metabolism in the liver of a drug taken orally before the drug reaches the systemic circulation.
Hypersensitivity Allergic or immune-mediated reaction to a drug, which can be serious, requiring airway maintenance or ventilatory assistance.
Idiosyncratic effect Abnormal or unexpected reaction to a drug, other than an allergic reaction, compared with the predicted effect.
Inhalation Taking a substance, typically in the form of gases, fumes, vapors, mists, aerosols, or dusts, into the body by breathing in.
Local effect Limited to the area of treatment (e.g., inhaled drug to treat constricted airways).
Lung availability/total systemic availability ratio (L/T ratio) Amount of drug that is made available to the lung out of the total available to the body.
Parenteral Administration of a substance in any way other than the intestine, most commonly an injection (e.g., intravenous, intramuscular, subcutaneous, intrathecal, or intraosseous).
Pharmacodynamics Mechanisms of drug action by which a drug molecule causes its effect in the body.
Pharmacogenetics Study of genetic factors and their influence on drug response.
Pharmacokinetics Time course and disposition of a drug in the body, based on its absorption, distribution, metabolism, and elimination.
Receptor Cell component that combines with a drug to change or enhance the function of the cell.
Structure–activity relationship (SAR) Relationship between a drug's chemical structure and the outcome it has on the body.
Synergism Drug interaction that occurs from two or more drug effects that are greater than if the drugs were given alone.
Systemic effect Pertains to the whole body, whereas the target for the drug is not local, possibly causing side effects (e.g., capsule of acetaminophen for a headache).
Tachyphylaxis Rapid decrease in response to a drug.
Therapeutic index (TI) Difference between the minimal therapeutic and toxic concentrations of a drug; the smaller the difference, the greater is the risk the drug will be toxic.
Tolerance Decreasing intensity of response to a drug over time.
Topical Use of the skin or mucous membrane (e.g., lotion).
Transdermal Use of the skin (e.g., patch).

The entire course of action of a drug, from dose to effect, can be understood in three phases: the drug administration, pharmacokinetic, and pharmacodynamic phases. This useful conceptual framework, based on the principles offered by Ariëns and Simonis,[1] organizes the steps of a drug's action from **drug administration** (method by which a drug dose is made available to the body) through effect and ultimate elimination from the body. This framework is illustrated in Fig. 2.1, which provides an overview of the interrelationship of the three phases of drug action, each of which is discussed in this chapter.

KEY POINT

Principles of drug action encompass three major topic areas: drug administration, pharmacokinetics, and pharmacodynamics.

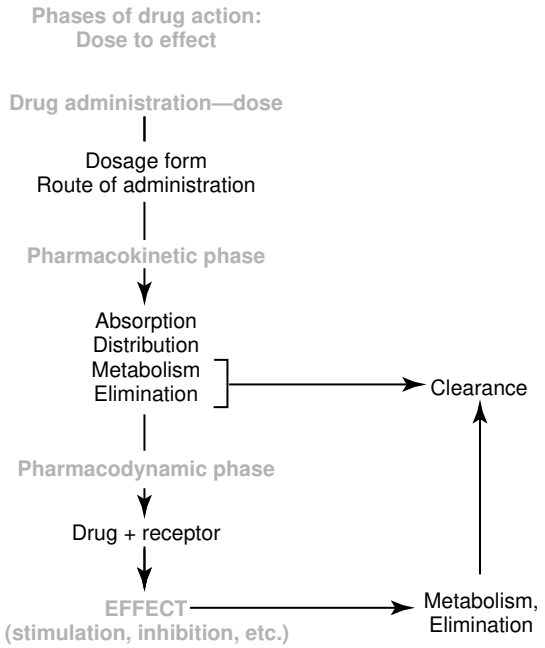
Drug Administration Phase

KEY POINT

The *drug administration* phase identifies drug dosage forms and routes of administration. The *pharmacokinetic phase* describes the factors determining drug absorption, distribution in the body, metabolism, breakdown of the active drug to its metabolites, and elimination of the active drug and inactive metabolites from the body.

Drug Dosage Forms

The drug administration phase entails the interrelated concepts of drug formulation (e.g., compounding a tablet for particular



• **Fig. 2.1** Conceptual scheme illustrating the major phases of drug action in sequence, from dose administration to effect in the body. (From Katzung, B.G., Masters, S.B., & Trevor, A.J. (Eds.) (2012). *Basic and Clinical Pharmacology* (12th ed.). New York: McGraw Hill Medical.)

dissolution properties) and drug delivery (e.g., designing an inhaler to deliver a unit dose). Two key topics of this phase are the drug dosage form and the route of administration. The *drug dosage form* is the physical state of the drug in association with nondrug components. Tablets, capsules, and injectable solutions are common drug dosage forms. The *route of administration* is the portal of entry for the drug into the body, such as oral (enteral), injection, or inhalation. The form in which a drug is available must be compatible with the route of administration preferred. The injectable route (e.g., intravenous route) requires a liquid solution of a drug, whereas the oral route can accommodate capsules, tablets, or liquid solutions. Some common drug formulations for each of the common routes of drug administration are listed in Table 2.1.

Drug Formulations and Additives

A drug is the active ingredient in a dosage formulation, but it is usually not the only ingredient in the total formulation. For example, in a capsule of an antibiotic, the capsule itself is a gelatinous material that allows for swallowing of the drug. The capsule material disintegrates in the stomach, and the active drug ingredient is released for absorption. The rate at which the active drug is liberated from a capsule or tablet can be controlled during the formulation process by altering drug particle size or by using a specialized coating or formulation matrix. Aerosolized agents for inhalation and treatment of the respiratory tract also contain ingredients other than the active drug, such as preservatives, propellants for metered dose inhaler (MDI) formulations, dispersants (surfactants), and carrier agents for dry powder inhalers (DPIs). Table 2.2 presents the various formulations with different ingredients for the beta (β)-adrenergic bronchodilator albuterol. In the nebulizer solution, benzalkonium chloride is a preservative, and sulfuric acid adjusts the pH of the solution. In the hydrofluoroalkane (HFA)-MDI, a hydrofluoroalkane is used as a propellant.

TABLE 2.1 Common Drug Formulations for Various Routes of Administration

Enteral	Parenteral	Inhalation	Transdermal	Topical
Tablet	Solution	Gas	Patch	Powder
Capsule	Suspension	Aerosol	Paste	Lotion
Suppository	Depot	—	—	Ointment
Elixir	—	—	—	Solution
Suspension	—	—	—	—

TABLE 2.2 Three Different Dosage Forms for the Bronchodilator Drug Albuterol, Indicating Ingredients Other Than Active Drug

Dosage Form	Active Drug	Ingredients
Nebulizer solution	Albuterol sulfate	Benzalkonium chloride, sulfuric acid
Respimat	Albuterol-ipratropium	Benzalkonium chloride, edetate disodium hydrochloric acid
Tablets	Albuterol sulfate	Lactose, butylparaben, sugar
MDI-HFA	Albuterol	1,1,1,2-Tetrafluoroethane, ethanol, oleic acid

HFA, Hydrofluoroalkane; *MDI,* metered dose inhaler.

Routes of Administration

Advances in drug formulation and delivery systems have yielded a wide range of routes by which a drug can be administered. In the following discussion, routes of administration have been divided into five broad categories: enteral, parenteral, transdermal, inhalation, and topical.

Enteral

The term **enteral** refers literally to the small intestine, but the enteral route of administration is more broadly applicable to administration of drugs intended for absorption anywhere along the gastrointestinal tract. The most common enteral route is by mouth (oral) because it is convenient, is painless, and offers flexibility in possible dosage forms of the drug, as shown in Table 2.1. The oral route requires the patient to be able to swallow; therefore airway-protective reflexes should be intact. If the drug is not destroyed or inactivated in the stomach and can be absorbed into the bloodstream, distribution throughout the body and a **systemic effect** can be achieved. Other enteral routes of administration include suppositories inserted in the rectum, tablets placed under the tongue (sublingual), and drug solutions introduced though an indwelling gastric tube.

Parenteral (Injectable)

Technically, the term **parenteral** means "besides the intestine," which implies any route of administration other than enteral. However, the parenteral route commonly refers to injection of a drug. Various options are available for injection of a drug, the most common of which are the following:

- *Intravenous (IV):* Injected directly into the vein, allowing nearly instantaneous access to systemic circulation. Drugs can be given as a bolus, in which case the entire dose is given rapidly, leading to a sharp increase in the drug's plasma concentration, or a steady infusion can be used to avoid this precipitous increase.
- *Intramuscular (IM):* Injected deep into a skeletal muscle. Because the drug must be absorbed from the muscle into the systemic circulation, the drug effects occur more gradually than with intravenous injection, although typically more rapidly than by the oral route.
- *Subcutaneous (SC):* Injected into the subcutaneous tissue beneath the epidermis and the dermis.
- *Intrathecal (IT):* Injected into the arachnoid membrane of the spinal cord to diffuse throughout the spinal fluid.
- *Intraosseous (IO):* Injected into the marrow of the bone.

Transdermal

An increasing number of drugs are being formulated for application to the skin (i.e., **transdermal** administration) to produce a systemic effect. The advantage of this route is that it can supply long-term continuous delivery to the systemic circulation. The drug is absorbed percutaneously, obviating the need for a hypodermic needle and decreasing the fluctuations in plasma drug levels that can occur with repeated oral administration.

Inhalation

Drugs can be given by **inhalation** for either a systemic effect or a local effect in the lung. Two of the most common drug

formulations given by this route are gases, which usually are given by inhalation for anesthesia (a systemic effect), and aerosolized agents intended to target the lung or respiratory tract in the treatment of respiratory disease (**local effect**). The technology and science of aerosol drug delivery to the respiratory tract continue to develop and are described in detail in Chapter 3. Box 2.1 provides a summary of devices commonly used for inhaled aerosol drug delivery. The general rationale for aerosolized drug delivery to the airways for treating respiratory disease is the local delivery of the drug to the target organ, with reduced or minimal body exposure to the drug and, it is hoped, reduced prevalence or severity of possible side effects.

Topical

Drugs can be applied directly to the skin or mucous membranes to produce a local effect. Such drugs are often formulated to minimize systemic absorption. Examples of **topical** administration include the application of corticosteroid cream to an area of contact dermatitis (e.g., poison ivy rash), administration of an eye drop containing a β-adrenergic antagonist to control glaucoma, and instillation of nasal drops containing an α-adrenergic agonist to relieve congestion.

Pharmacokinetic Phase

The term pharmacokinetic phase refers to the time course and disposition of a drug in the body, based on its absorption, distribution, metabolism, and elimination. Once presented to the body, as described in the drug administration phase, a drug crosses local anatomic barriers to varying extents, depending on its chemical properties and the physiologic environment of the body compartment it occupies. For a systemic effect, it is desirable for the drug to get into the bloodstream for distribution throughout the body; for a local effect, this is not desirable and can lead to unwanted side effects throughout the body. Absorption, distribution, metabolism, and elimination are the factors influencing and determining the course of a drug after it is introduced to the body. In essence, **pharmacokinetics** describes what the body does to a drug, and **pharmacodynamics** describes what the drug does to the body.

Absorption

When given orally for a systemic effect, a pill must first dissolve to liberate the active ingredient. The free drug must then reach the epithelial lining of the stomach or intestine and traverse the lipid membrane barriers of the gastric and vascular cells before reaching the bloodstream for distribution throughout the body. The lining of the lower respiratory tract also presents barriers to drug absorption. This mucosal barrier consists of five identifiable elements:

1. Airway surface liquid
2. Epithelial cells
3. Basement membrane
4. Interstitium
5. Capillary vascular network

After traversing these layers, a drug can reach the smooth muscle or glands of the airway. The mechanisms by which drugs move across membrane barriers include aqueous diffusion, lipid diffusion, active or facilitated diffusion, and pinocytosis. Generally, a drug must be sufficiently water soluble to reach a lipid (cell) membrane and sufficiently lipid soluble to diffuse across the cell barrier. Fig. 2.2 illustrates these basic mechanisms.

Aqueous Diffusion

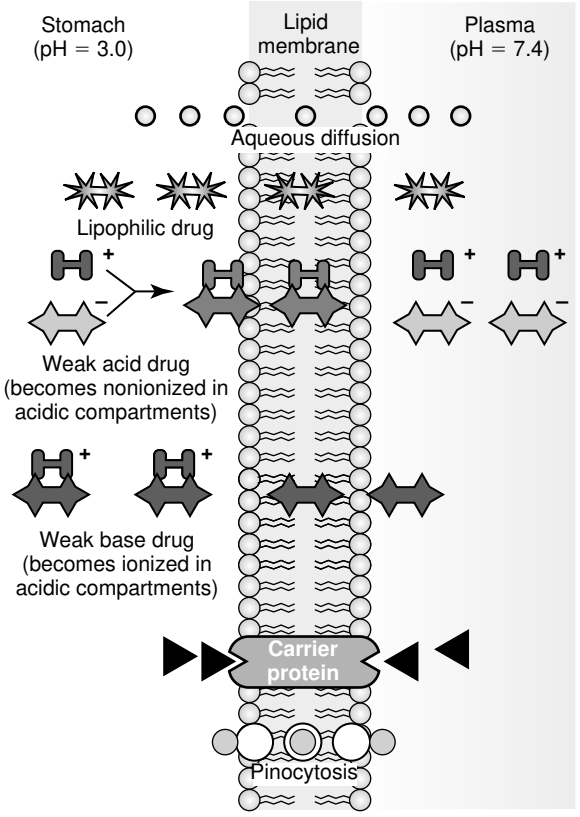
Aqueous diffusion occurs in the aqueous compartments of the body, such as the interstitial spaces or the space within a cell. Transport across epithelial linings is restricted because of small pore size; capillaries have larger pores, allowing passage of most drug molecules. Diffusion occurs by a concentration gradient.

Lipid Diffusion

Lipid diffusion is an important mechanism for drug absorption because of the many epithelial membranes that must be crossed if a drug is to distribute in the body and reach its target organ. Epithelial cells have lipid membranes, and a drug must be lipid

• BOX 2.1 Devices for Inhaled Administration of Drugs

- Vaporizer (anesthetic gases)
- Atomizer
- Nebulizer, small or large
- Metered dose inhaler (MDI), with or without spacer
- Respimat soft mist inhaler
- Dry powder inhaler (DPI)
- Ultrasonic nebulizer (USN)



• Fig. 2.2 Pathways by which drugs can traverse lipid membranes and enter the circulation. A membrane separating an acidic compartment (stomach) and a neutral compartment (plasma) is shown to illustrate that only the nonionized forms of weak acids or weak bases cross these lipophilic barriers more readily than ionized forms.

soluble (nonionized, nonpolar) to diffuse across such a membrane. Lipid-insoluble drugs tend to be ionized, that is, have positive and negative charges separated on the molecule (polar), and are water soluble.

Many drugs are weak acids or weak bases, and the degree of ionization of these molecules is dependent on the pK_p (the pH at which the drug is 50% ionized and 50% nonionized), the ambient pH, and whether the drug is a weak acid or base. The direction of increasing ionization is opposite for weak acids and weak bases while the ambient pH changes.

Weak acid: Because an acid contributes protons (H^+ ions), the protonated form is neutral, or nonionized.

$$\text{Drug}_{\text{neutral}} \leftrightarrow \text{Drug}^- \text{ anion} + H^+ \text{ Proton (protonated)}$$

$$\text{Drug}^+ \text{ cation} \leftrightarrow \text{Drug}_{\text{neutral}} + H^+ \text{ Proton (protonated)}$$

Weak base: Because a base accepts protons (hydrogen [H^+] ions), the unprotonated form is neutral, or nonionized.

- The protonated weak acid is neutralized by the addition of H^+ ions in an acidic environment, is nonionized, and is lipid soluble.
- The protonated weak base gains a charge by adding H^+ ions in an acidic environment, is ionized, and is not lipid soluble.

Fig. 2.2 conceptually illustrates the principle of lipid diffusion and absorption for weak acids and bases.

Some drugs, such as ethanol, are neutral molecules and are always nonionized. They are well absorbed into the bloodstream and across the blood–brain barrier. Other drugs, such as ipratropium bromide and *d*-(+)-tubocurarine, are quaternary amines, have no unshared electrons for reversible binding of H^+ ions, and are permanently positively charged. Ipratropium is not lipid soluble and does not absorb and distribute well from the mouth or the lung with oral inhalation. A secondary or tertiary amine, such as atropine, can give up its H^+ ion and become nonionized, increasing its absorption, distribution, and consequent side effects in the body.

Carrier-Mediated Transport

Special carrier molecules embedded in the lipid membrane can transport some substances, such as amino acids, sugars, or naturally occurring peptides, and the drugs that resemble these substances. In some instances, a drug can compete with the endogenous substance normally transported by the carrier.

Pinocytosis

Pinocytosis refers to the incorporation of a substance into a cell by a process of membrane engulfment and transport of the substance within vesicles, allowing translocation across a membrane barrier.

Factors Affecting Absorption

The route of administration determines which barriers to absorption must be crossed by a drug. These barriers can affect the drug's time to onset and time to peak effect. Intravenous administration bypasses the need for absorption from the gastrointestinal tract seen with oral administration, generally gives a very rapid onset and peak effect, and provides 100% availability of the drug in the bloodstream. The term **bioavailability** indicates the proportion of a drug that reaches the systemic circulation. For example, the bioavailability of oral morphine is 0.24 because only about a quarter of the morphine ingested actually arrives in the systemic circulation. Bioavailability is influenced not only by absorption but also by inactivation caused by stomach acids and by metabolic degradation, which can occur before the drug reaches the main systemic compartment. Another important variable governing absorption and bioavailability is blood flow to the site of absorption.

Distribution

To be effective at its desired site of action, a drug must have a certain concentration. An antibiotic is investigated for its *minimal inhibitory concentration (MIC)*—the lowest concentration of a drug at which a microbial population is inhibited. *Drug distribution* is the process by which a drug is transported to its sites of action, is eliminated, or is stored. When given intravenously, most drugs distribute initially to organs that receive the most blood flow. After this brief initial distribution phase, subsequent phases of distribution occur on the basis of the principles of diffusion and transport outlined earlier and the drug's physical and chemical nature and ability to bind to plasma proteins. The initial distribution phase is clinically important for lipophilic anesthetics (e.g., propofol and thiopental) because they produce rapid onset of anesthesia as a function of the high blood flow to the brain, and their effects are quickly terminated during redistribution to other tissues. The binding of drugs to plasma proteins can also be clinically relevant in rare instances, such as when a large portion of a drug is inactive because it is bound to plasma proteins but subsequently becomes displaced (and, thus, active) by a second drug that binds to the same proteins.

The plasma concentration of a drug is partially determined by the rate and extent of absorption versus the rate of elimination for a given dose amount. The volume of the compartment in which the drug is distributed also determines the concentration achieved in plasma. Compartments and their approximate volumes in a 70-kg adult are given in Table 2.3.

Volume of Distribution

Suppose a certain drug that distributes exclusively in the plasma compartment is administered intravenously. If a 10-mg bolus of the drug is given, and the volume of the patient's plasma compartment is 5 L, the concentration in the plasma (barring degradation or elimination) would be 2 mg/L. In this simple example, the *volume of distribution (V_D)* is the same as the volume of the plasma compartment. In practice, drug distribution is usually more complex, and the actual tissue compartments occupied by the drug are unknown. Nonetheless, V_D describes a useful mathematical equation relating the total amount of drug in the body to the plasma concentration:

$$\text{Volume of distribution } (V_D) = \frac{\text{Drug amount}}{\text{Plasma concentration}}$$

TABLE 2.3 Volumes (Approximate) of Major Body Compartments

Compartment	Volume (L)
Vascular (blood)	5
Interstitial fluid	10
Intracellular fluid	20
Fat (adipose tissue)	14–25

EXAMPLE

If 350 mg of theophylline results in a concentration in the plasma of 10 mg/L (equivalent to 10 mcg/mL), the volume of distribution (V_D) is calculated as:

$$V_D = \frac{350\ \text{mg}}{10\ \text{mg/L}}$$

$$V_D = 35\ \text{L}$$

The drug can be absorbed and distributed into sites other than the vascular compartment, which is only approximately 5 L, and the calculated volume of distribution can be much larger than the blood volume, as in the case of theophylline, which has a V_D of 35 L in a 70-kg adult. For this reason, V_D is referred to as the *apparent volume of distribution* to emphasize that V_D does not refer to an actual physiologic space. Some drugs, such as fluoxetine (an antidepressant) and inhaled anesthetics, are sequestered in peripheral tissues and can have apparent volumes of distribution many times greater than the entire volume of the body.

In a clinical setting, V_D is rarely measured but is, nonetheless, important for estimating the dose needed to achieve a given therapeutic level of a drug. By rearranging the equation for V_D, the drug amount should equal the V_D multiplied by the concentration.

EXAMPLE

To achieve a theophylline concentration of 15 mg/L with a V_D of 35 L, we calculate a dose of:

$$\text{Drug amount (drug dose)} = \text{Plasma concentration} \times V_D$$

$$\text{Dose} = 15\ \text{mg/L} \times 35\ \text{L}$$

$$\text{Dose} = 525\ \text{mg}$$

The following points should be noted:

- The preceding calculation assumes that the dose is completely available to the body. This may be true if a dose is given intravenously, but there may be less than 100% bioavailability if a dose is given orally.
- This is a *loading dose,* and subsequent doses to maintain a level of concentration depend on the rate of absorption versus the rates of metabolism and excretion (discussed in the next sections).
- V_D may change as a function of age or disease state.
- The concept of V_D is not directly helpful in topical drug administration and delivery of aerosolized drugs intended to act directly on the airway surface. V_D for topical deposition in the airway is not measured, and the drug is deposited locally in the respiratory tract, and some drugs are absorbed from the airway into blood.

Metabolism

KEY POINT

The liver is a primary site of drug metabolism and biotransformation, and the kidneys are the primary site of drug excretion, although both drugs and metabolites can also be excreted in feces.

The processes by which drug molecules are metabolized, or biotransformed, constitute a complex area of biochemistry that is beyond the scope of this text. Common pathways for the biotransformation of drugs are listed in Box 2.2. Generally, phase 1 biochemical reactions convert the active drug to a more polar (water-soluble) form, which can be excreted by the kidney. Drugs that are transformed in a phase 1 reaction may be transformed further in a phase 2 reaction, which combines (conjugates) a substance (e.g., glucuronic acid) with the metabolite to form a highly polar conjugate. In the case of some drugs, biotransformation is accomplished by just phase 1 or phase 2 metabolism without prior transformation by the other phase. Metabolites are often less biologically active than the parent drug. Nevertheless, some drugs are inactive until metabolized (e.g., enalapril) or produce metabolites that are more toxic than their progenitors (e.g., breakdown products of acetaminophen).

Site of Drug Biotransformation

The liver is the principal organ for drug metabolism, although other tissues, including the lung, intestinal wall, and endothelial vascular wall, can transform or metabolize drugs. For example, epinephrine, a weak base, is absorbed into the intestinal wall, where sulfatase enzymes inactivate it as the drug diffuses into the circulation. The liver contains intracellular enzymes that usually convert lipophilic (lipid-soluble) drug molecules into water-soluble metabolites that are more easily excreted. The major enzyme system in the liver is the cytochrome P450 oxidase system (CYP). There are many forms of cytochrome P450, which are hemoproteins with considerable substrate versatility and the ability to metabolize new drugs or industrial compounds. The various forms of cytochrome P450 have been divided into about a dozen subcategories, termed *isoenzyme families.* The four most important isoenzyme families for drug metabolism have been designated *CYP1, CYP2, CYP3,* and *CYP4.* A given drug may be metabolized predominantly by only one member of an isoenzyme family, whereas another drug may be metabolized by multiple enzymes in the same family or by several distinct enzymes across families. Knowing which particular CYP enzyme metabolizes a drug may be important for predicting drug interactions, as further described subsequently.

Enzyme Induction and Inhibition

Chronic administration or abuse of drugs that are metabolized by the enzyme systems in the liver can induce (increase) or inhibit the levels of the enzymes (enzyme induction and inhibition). Examples of drugs or agents that can induce or inhibit CYP enzymes are listed in Table 2.4.

• BOX 2.2 Common Pathways for Drug Metabolism

Phase 1

- Oxidative hydroxylation
- Oxidative dealkylation
- Oxidative deamination
- N-oxidation
- Reductive reactions
- Hydrolytic reactions (e.g., esterase enzymes)

Phase 2

- Conjugation reactions (e.g., glucuronide or sulfate)

Enzyme induction can affect the therapeutic doses of drugs required. Rifampin can induce CYP enzymes and increase the metabolism of several drugs, including warfarin and oral contraceptives. Likewise, cigarette smoking can increase the breakdown of theophylline in patients with chronic lung disease, shortening the half-life of the drug from approximately 7.0 to 4.3 hours. Dosages would need to be adjusted accordingly to maintain a suitable plasma level of theophylline. Conversely, a substantial portion of drug interactions involves inhibition of CYP enzymes. A given drug is not likely to inhibit all the CYP isoenzymes equally. For example, the antibiotic ciprofloxacin is a potent inhibitor of an enzyme in the CYP family that also metabolizes theophylline. Coadministration of ciprofloxacin with theophylline can increase theophylline levels—the opposite effect of cigarette smoking.

TABLE 2.4 Drugs Causing Induction or Inhibition of Cytochrome P450 Enzymes

Cytochrome P450 Isoenzyme	Inducers	Inhibitors
CYP1A2	Phenytoin	Ciprofloxacin
	Rifampin	Diltiazem
CYP2D6		Ranitidine
		Fluoxetine
CYP3A4	Carbamazepine	Diltiazem
	Corticosteroids	Fluoxetine
	Rifampin	Erythromycin

CYP, Cytochrome P450 oxidase system.

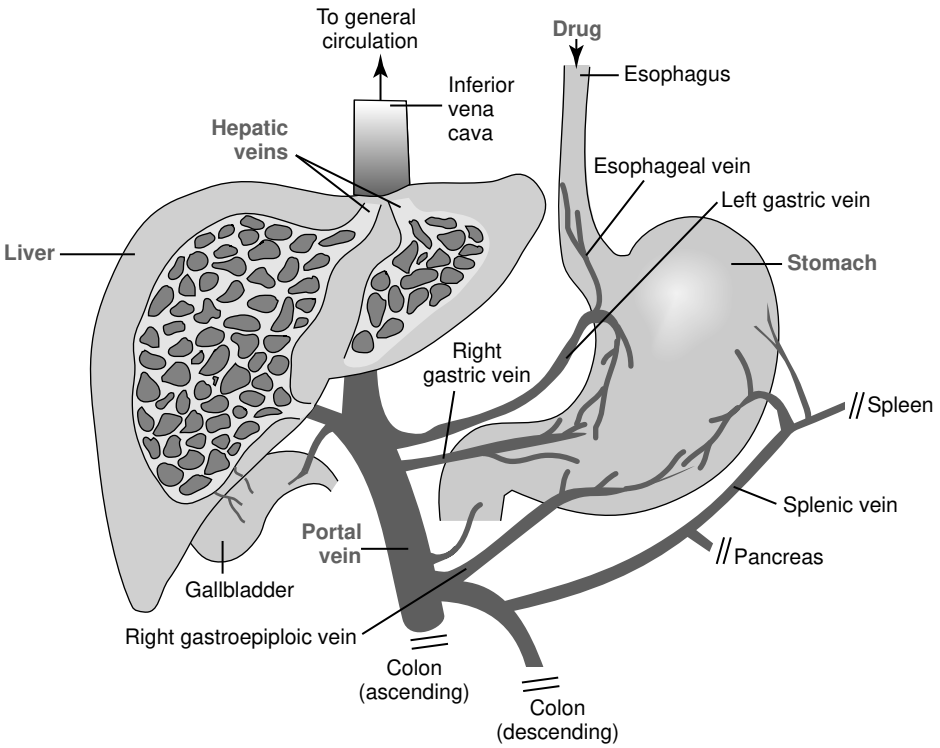
First-Pass Effect

Another clinically important effect of the liver on drug metabolism is referred to as the **first-pass effect** of elimination. When a drug is taken orally and absorbed into the blood from the stomach or intestine, the portal vein drains this blood directly into the liver (Fig. 2.3). Blood is drained from the liver by the right and left hepatic veins directly into the inferior vena cava and on into the general circulation.

If a drug is highly metabolized by the liver enzymes and is administered orally, most of the drug's activity is terminated in its passage through the liver before it ever reaches the general circulation and the rest of the body. This is the first-pass effect. Examples of drugs with a high first-pass effect are propranolol; nitroglycerin (sublingual administration is preferred to oral administration); and fluticasone propionate, an aerosolized corticosteroid. The first-pass effect causes difficulties with oral administration that must be overcome by increasing the oral dose (compared with the parenteral dose) or by using a delivery system that circumvents first-pass metabolism. The following routes avoid first-pass circulation through the liver: injection, buccal or sublingual (e.g., tablets), transdermal (e.g., patch), rectal (e.g., suppositories), and inhalation. These routes of administration bypass the portal venous circulation, allowing drugs to be generally distributed in the body before being circulated through the liver and ultimately metabolized. They also bypass metabolic degradation occurring in the gut as a result of specific metabolic enzymes (e.g., CYP3) or bacterial flora.

Elimination

The primary site of drug excretion in the body is the kidney, just as the liver is the site of the majority of drug metabolism. The kidney is important for removing the drug metabolites produced by the liver. Some drugs are not metabolized and are eliminated



• **Fig. 2.3** Anatomy of venous drainage from the stomach that forms the basis for the first-pass effect of orally administered drugs.

from the circulation entirely by the kidney. The route of elimination becomes important when choosing between alternative therapies because liver or kidney disease can alter the clearance of a drug by these organs. Generally, *clearance* is a measure of the ability of the body to rid itself of a drug. Most often, clearance is expressed as *total systemic* or *plasma clearance* to emphasize that all of the various mechanisms by which a given drug is cleared (e.g., metabolism, excretion) are taken into account.

Plasma Clearance

The term V_D is an abstraction does not usually correspond to any real physiologic volume, and similarly, the term *plasma clearance (Cl_p)* refers to a hypothetical volume of plasma that is completely cleared of a drug over a given period. Consequently, Cl_p is usually expressed as liters per hour (L/hr) or, if body weight is taken into account, liters per hour per kilogram (L/hr/kg). Because Cl_p gives an indication of the quantity of drug removed from the body over a given period, it can be used to estimate the rate at which a drug must be replaced to maintain a steady plasma level.

Maintenance Dose

To achieve a steady level of drug in the body, dosing must equal the rate of elimination:

$$\text{Dosing rate (mg/hr)} = (CI_P)(\text{L/hr}) \times \text{Plasma concentration (mg/L)}$$

EXAMPLE

The clearance of theophylline is given as 2.88 L/hr/70 kg. For an average 70-kg adult, to maintain a plasma drug level of 15 mg/L (equivalent to 15 mcg/mL), calculate the dosing rate as follows:

$$\text{Dosingrate} = 2.88\,\text{L/hr} \times 15\,\text{mg/L} = 43.2\,\text{mg/hr}$$

The preceding simplified calculation assumes total bioavailability of the drug, which may not be true for some routes of administration, and is intended for conceptual illustration only. Actual patient treatment must take other factors into account. The drug could be given by constant infusion or divided into dosing intervals (e.g., where half the daily dose is given every 12 hours). When deciding on a dosing interval, it is desirable to know the *plasma half-life.*

Plasma Half-Life

The *plasma half-life ($T\frac{1}{2}$)* (the time required for the plasma concentration of a drug to decrease by one half) is a measure of how quickly a drug is eliminated from the body. More pertinent to dosing schedules, however, $T\frac{1}{2}$ indicates how quickly a drug can accumulate and reach steady-state plasma levels. Drugs with a short $T\frac{1}{2}$ (e.g., amoxicillin) reach steady-state levels quickly and must be given more frequently to maintain plasma levels, whereas the opposite is true of drugs with a long $T\frac{1}{2}$, such as digoxin. Table 2.5 lists selected drugs in common use with their plasma half-lives.

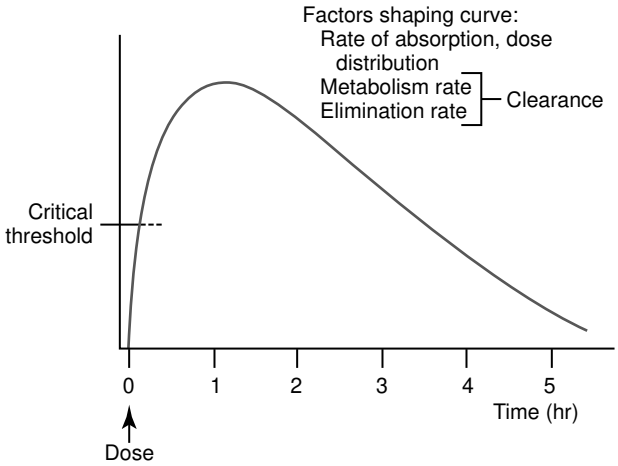
Time–Plasma Curves

The concentration of a drug in the plasma over time can be graphed as a time–plasma curve (Fig. 2.4). The shape of this curve describes the interplay of the kinetic factors of absorption, distribution, metabolism, and elimination. These curves can indicate whether the dose given is sufficient to reach and maintain the critical threshold of concentration needed to achieve the desired therapeutic effect. Such a curve can also be plotted for concentrations of an aerosol drug in respiratory tract secretions. However, the duration of the *clinical effect,* rather than the concentration of the drug, is often represented in studies of aerosol drugs, particularly bronchodilators. The clinical effect is more helpful than a blood level in describing the pharmacokinetics of inhaled aerosols, which rely on topical delivery with a local effect in the airway.

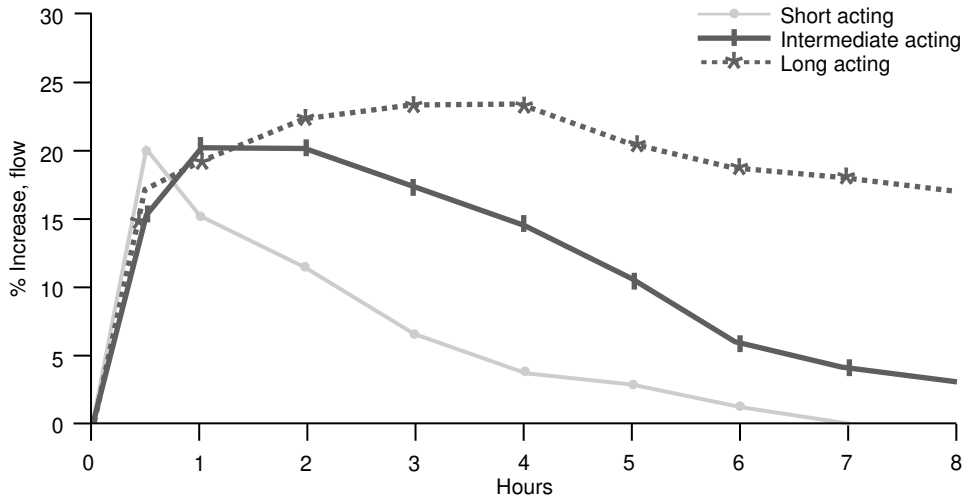
Fig. 2.5 illustrates hypothetical curves for the peak effect and duration of effect of three bronchodilator drugs on expiratory flow rates. The short-acting curve could represent a drug, such as racemic epinephrine, an ultrashort-acting catecholamine bronchodilator. On the basis of its time curve, this agent is too short acting for maintenance therapy and is not β receptor specific. The intermediate curve could represent such an agent as albuterol, which has a peak effect of 30 to 60 minutes by inhalation and a duration of action of approximately 4 to 6 hours. These kinetics are useful for as-required bronchodilation or for maintenance therapy if a patient needs the drug four times daily. The kinetics indicate that bronchodilation with albuterol, an intermediate-acting drug, would

TABLE 2.5 Plasma Half-Lives of Common Drugs

Drug	Half-Life (hr)
Acetaminophen	2.0
Amoxicillin	1.7
Azithromycin	40.0
Digoxin	39.0
Gabapentin	6.5
Morphine	1.9
Paroxetine	17.0
Terbutaline	14.0



• **Fig. 2.4** Plasma concentration of a drug over time. The critical threshold is the minimal level of drug concentration needed for a therapeutic effect.



• **Fig. 2.5** Hypothetical time–effect curves for three different bronchodilating agents, illustrating onset, peak effect, and duration.

not be maintained during an entire night. Finally, a long-acting agent, such as the bronchodilator salmeterol, could provide a 12-hour duration of effect, although time to peak effect is slower (<2 hours). These kinetics are useful for convenient twice-daily dosage and around-the-clock bronchodilation. This example illustrates how pharmacokinetics of an inhaled aerosol can help determine the choice of a particular drug for a given clinical application and the dosage schedule needed to achieve the therapeutic effect. Other factors in the choice of a drug, whether inhaled aerosol, oral, or injectable, include the side effect profile, the individual's reaction to the drug, allergies, and compliance factors (patient adherence to dosage instructions), such as delivery formulations and dose timing.

Pharmacokinetics of Inhaled Aerosol Drugs

The inhalation route used for therapeutic aerosols, together with the physicochemical nature of the drug, determines the absorption, distribution, metabolism, and elimination of the aerosol drug.

Local versus Systemic Effect

Inhaled aerosols are deposited on the surface of the upper or lower airway and are a form of topically administered drug. As topically deposited agents, inhaled aerosols can be intended either for a local effect in the upper or lower airway or for a systemic effect because the drug is absorbed and distributed in blood. A *local effect* is exemplified by a nasally inhaled vasoconstricting agent (decongestant), such as oxymetazoline (Afrin), or by an inhaled bronchodilator aerosol, such as albuterol (Proventil-HFA, Ventolin-HFA, Proair HFA). A systemic effect might be exemplified by the administration of inhaled zanamivir (Relenza) to treat influenza, inhaled morphine for pain control, or inhaled insulin aerosol for systemic control of diabetes.[2]

Inhaled Aerosols in Pulmonary Disease

Inhaled aerosols used in the treatment of respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), or cystic fibrosis (CF), are intended for a local, targeted effect in the lung and airway. The rationale for the inhalation route in therapy of the lung is to maximize lung deposition while minimizing body (systemic) exposure and unwanted side effects. If the ratio of drug in the lung is high relative to the amount of drug in the overall body (systemic drug level), the inhalation route offers an advantage over direct systemic administration (oral, intravenous) in treating the lung.

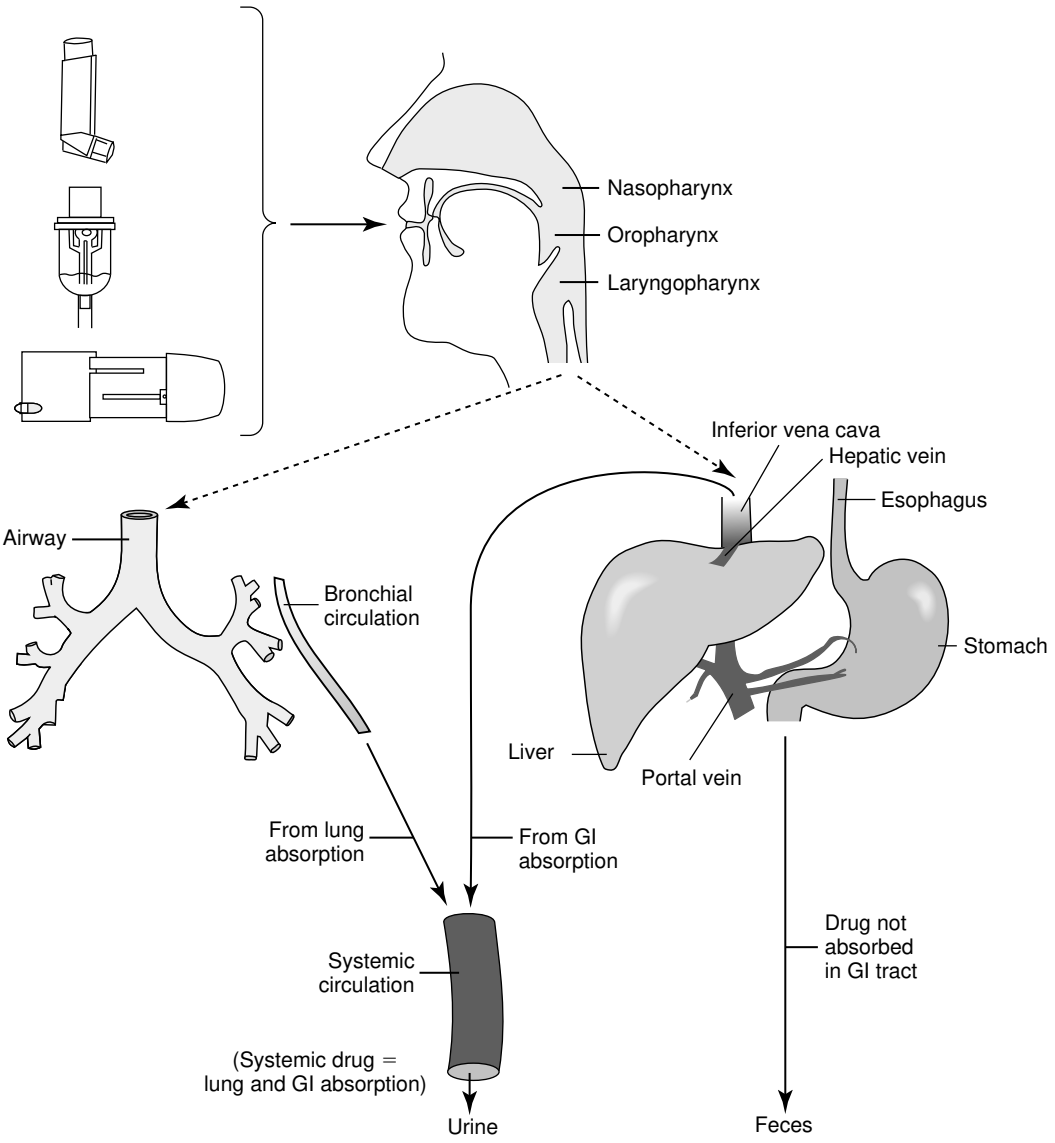
Distribution of Inhaled Aerosols

KEY POINT

The inhaled route of administration can involve both gastrointestinal and lung distributions. The systemic level of an inhaled drug and possible extrapulmonary side effects depend on both gastrointestinal and lung absorption of the active drug.

Because a portion of an inhaled aerosol is swallowed, the inhalation route leads to gastrointestinal absorption as well as lung absorption of the drug (Fig. 2.6). After inhalation of an aerosol by a spontaneously breathing patient without the use of artificial airway, a proportion of the aerosol exerts an impact in the oropharynx and is swallowed, and a proportion is inhaled into the airway. The traditional percentages given for stomach and airway proportions, based on Newman's classic measures[3] in 1981 with an MDI, are approximately 90% (stomach) and 10% (airway). Similar percentages have been found with other aerosol delivery devices; however, newer devices are able to deliver more to the airway, assuming use of good technique.

Approximately 50% to 60% of the drug impacts in the mouth or oropharynx and contributes to the 90% reaching the stomach. These amounts are used in discussing the pathways of metabolism for an inhaled drug. Although the remaining 10% is traditionally accepted as the proportion of inhaled drug that reaches the lower respiratory tract when delivered via currently available devices, the exact percentage can vary from 10% to 30% with different delivery devices or techniques of patient use. Lung deposition with an inhaled corticosteroid, budesonide (Pulmicort), has been reported as 15% with a pressurized MDI (pMDI) and 32% with a DPI[4] (Pulmicort Turbuhaler; AstraZeneca, Wilmington, DE). Use of reservoir devices with MDIs or delivery through endotracheal tubes can significantly change oropharyngeal impaction or airway delivery (see Chapter 3).



• **Fig. 2.6** Orally inhaled aerosol drugs distribute to the respiratory tract and to the stomach through swallowing of oropharyngeally deposited drug. *Top left:* Inhalation devices include metered dose inhaler *(top),* nebulizer *(middle),* and dry powder inhaler *(bottom). GI,* Gastrointestinal.

Oral Portion (Stomach). The swallowed aerosol drug is subject to gastrointestinal absorption, distribution, and metabolism, just like an orally administered drug. The aerosol drug can be absorbed from the stomach and metabolized in the liver (see Fig. 2.6), producing a first-pass effect. The drug may also be inactivated in the intestinal wall as it is absorbed into the portal circulation. The site of absorption in the gastrointestinal tract is determined by the principles governing diffusion of drugs through lipid membranes. Generally, if the first-pass metabolism is high, systemic levels are only caused by lung absorption; if the first-pass metabolism is low and the drug is swallowed, there is a higher systemic level from gastrointestinal tract absorption, which may increase side effects in the body. The first-pass metabolism of three common inhaled aerosol drugs is as follows:

- Albuterol: 50%
- Budesonide: 90%
- Terbutaline: 90%
- Fluticasone: 99%
- Ciclesonide: 99%

Inhaled Portion. It is thought that aerosol drugs interact with the site of action in the airway: secretions in the lumen, nerve endings, cells (e.g., mast cells), or bronchial smooth muscle in the airway wall. The drug may be subsequently absorbed into the bronchial circulation, which drains into the right and left atria of the heart and then into the systemic circulation. The exact mechanism by which an aerosol drug, such as a bronchodilator, reaches the appropriate receptors to exert an effect is not well known. If the inhaled drug is not removed by mucociliary action or locally inactivated, the drug may be absorbed, and this increases the systemic availability of the drug.

Lung Availability/Total Systemic Availability Ratio

KEY POINT

The sources of the total systemic level of a drug are quantified in the lung availability/total systemic availability ratio (L/T ratio)—the higher the ratio, the greater is the systemic drug level available from the lung, as a result of efficient lung delivery, high first-pass metabolism, or both.

The **lung availability/total systemic availability ratio (L/T ratio)** quantifies the efficiency of aerosol drug delivery to the lung and is based on the distribution to the airway and gastrointestinal tract just described. For an aerosol drug (e.g., a bronchodilator or corticosteroid) that targets the respiratory tract, the L/T ratio can be defined as the proportion of drug available from the lung, out of the total systemically available drug.

The *clinical* or *therapeutic effect* of a bronchoactive aerosol comes from the inhaled drug deposited in the airways. The *systemic* or *extrapulmonary side effects* come from the total amount of drug absorbed into the system. The total systemic drug level is caused by airway absorption plus the amount absorbed from the gastrointestinal tract. The L/T ratio can quantify and compare the efficiency of drug delivery systems targeting the respiratory tract. Any action that reduces the swallowed portion of the inhaled drug, such as a reservoir device (spacer, holding chamber), or high first-pass metabolism, can increase the L/T ratio. Factors that can increase the L/T ratio are summarized in Box 2.3. A perfectly efficient inhalation device would deliver all of the drug to the lung and none to the oropharynx or gastrointestinal tract, giving a ratio of 1 (lung availability = total systemic availability; all systemic drug comes only from the lung absorption).

CLINICAL CONNECTION

A respiratory therapist (RT) can increase the L/T ratio by properly instructing the patient in the use of the aerosol device. Additionally, the use of a breath hold may increase L/T ratio by assisting in deposition of aerosol particles.

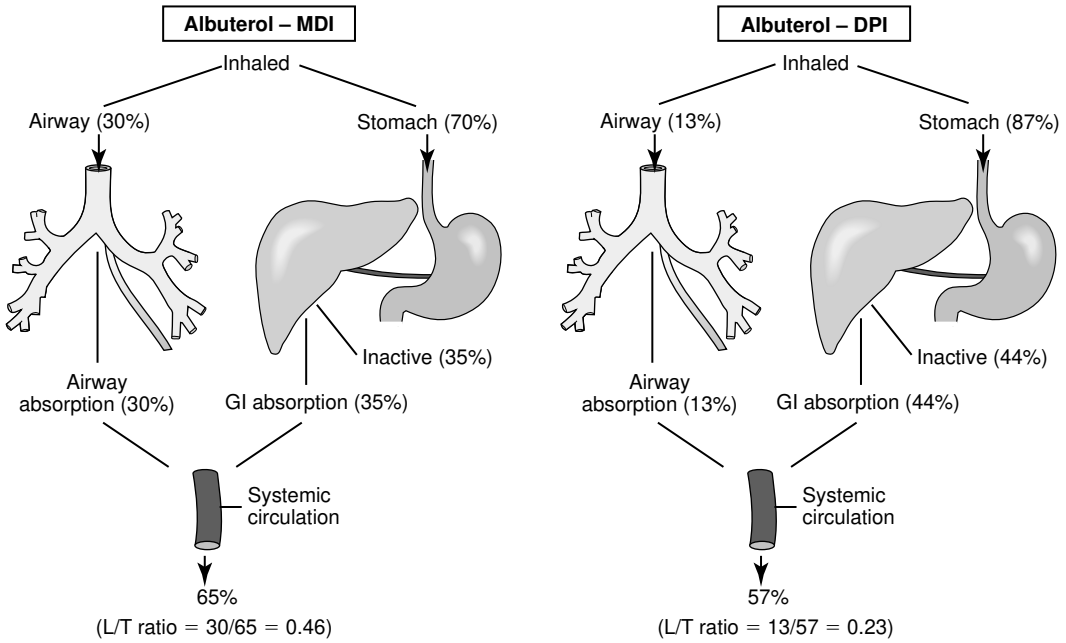
This concept was proposed in 1991 by Borgström[5] and elaborated on by Thorsson.[6] An example, based on the data of Thorsson for albuterol inhalation using two different delivery devices, is given in Fig. 2.7. With use of an MDI, approximately 30% of the inhaled drug reaches the lung, with 70% going to the stomach. With complete absorption from the stomach, half of this 70% is broken down in the liver so that 35% reaches the systemic circulation. The total amount of the original 100% dose reaching the circulation is 65% (lung, 30%; stomach and liver, 35%). Because 30% of the 65% comes from the lung, this gives an L/T ratio of 30/65 = 0.46.

The data for the DPI, using a Rotahaler (GlaxoSmithKline, Research Triangle Park, NC), which is no longer available, give an L/T ratio of 0.23 (lung, 13%; stomach and liver, 44%). On the basis of these ratios, inhalation of albuterol via an MDI gives more efficient lung delivery with less systemic availability compared with inhalation via a DPI, such as the Rotahaler. With the MDI, 46% of the systemic exposure is from the lung, whereas with the DPI, 23% is from the lung. A high L/T ratio is desired; Table 2.6 gives examples of various L/T ratios, along with lung deposition for several drugs and delivery devices.

The L/T ratio is determined by the rate of first-pass metabolism and the efficiency of the inhalation device in placing the drug in the airway. A high L/T ratio can be achieved even with poor lung delivery and efficient stomach absorption if there is a high first-pass effect on the swallowed drug. Comparisons of L/T ratios must be between the *same* drugs with different delivery devices. Two drugs

• BOX 2.3 Factors Increasing Lung Availability/Total Systemic Availability Ratio With Inhaled Drugs

- Efficient delivery devices (high airway and low gastrointestinal delivery)
- Inhaled drugs with high first-pass metabolism
- Mouthwashing, including rinsing and spitting
- Use of a reservoir device (spacer, holding chamber) to decrease oropharyngeal deposition and swallowed drug amount



• **Fig. 2.7** The lung availability/total systemic availability *(L/T)* ratio can quantify the efficiency of aerosol drug delivery to the respiratory tract by partitioning relative amounts from the gastrointestinal tract and from the respiratory tract *(see text for explanation)*. *DPI,* Dry powder inhaler; *GI,* gastrointestinal; *MDI,* metered dose inhaler. (Data from Thorsson. L. (1995). Influence of inhaler systems on systemic availability, with focus on inhaled corticosteroids. *Journal of Aerosol Medicine,* 8(Suppl 3), S29.)

TABLE 2.6 Lung Availability/Total Systemic Availability Ratios for Several Inhaled Drugs With Various Aerosol Delivery Devices*

Drug	Device	Lung Deposition (%)	L/T Ratio	Subjects
Albuterol	pMDI	18.6	0.36	Patients—good coordinators
		7.2	0.17	Patients—poor coordinators
	BAI (pMDI)	20.8	0.41	Patients—poor coordinators
	Turbuhaler	23.2	0.45	Healthy volunteers
Budesonide	pMDI (CFC)	15	0.66	Healthy subjects
	Turbuhaler	32	0.87	Healthy subjects
	MDI (HFA)†	59	0.92	Patients

*All drug amounts are expressed as percentages of metered or nominal dose.
†Data from Harrison, L.I. (2002). Local versus total systemic bioavailability of beclomethasone dipropionate CFC and HFA metered dose inhaler formulations. *Journal of Aerosol Medicine,* 15, 401 [erratum (2003) in *Journal of Aerosol Medicine*,16, 97].
BAI, Breath-actuated inhaler; *CFC,* chlorofluorocarbon; *HFA,* hydrofluoroalkane; *L/T ratio,* lung availability/total systemic availability; *pMDI,* pressurized metered dose inhaler.
Data from Borgström, L. (1998). Local versus total systemic bioavailability as a means to compare different inhaled formulations of the same substance. *Journal of Aerosol Medicine,* 11, 55.

with different first-pass metabolism rates can have different L/T ratios even if the airway deposition or delivery device is the same. A good example is provided in Table 2.6, in the comparison of albuterol and budesonide, both administered via a Turbuhaler DPI. Albuterol and budesonide have first-pass metabolism rates of 50% and 90%, respectively. With approximately the same lung delivery of 22% to 23% for both drug–device systems, the L/T ratio is 0.45 for albuterol but 0.87 for budesonide. The improved L/T ratio of budesonide compared with albuterol is not caused by a difference in device efficiency but by the higher rate of metabolism of budesonide that reduces systemic blood levels from gastrointestinal absorption. The L/T ratio also suggests that aerosol delivery devices should be evaluated together with the drug to be used. "Each combination of active drug and device is a unique pharmaceutical formulation, as both the drug itself and the device can influence the overall properties of the formulation."[5] The L/T ratio does not determine whether systemic toxicity or side effects will occur. First, systemic effects depend on the amount of active drug absorbed into the system, whether from the lung or from the gastrointestinal tract. An inhaled corticosteroid, such as flunisolide, is rapidly metabolized in a first-pass effect. As a result, the swallowed portion gives minimal systemic levels. Good absorption of the aerosol drug from the lungs in sufficiently high doses could, however, cause systemic effects. Second, delivery to the oropharynx and gastrointestinal tract by a less efficient aerosol delivery device or method may be irrelevant if the drug is largely inactivated when taken orally and causes no local oropharyngeal effects. Catecholamine bronchodilators would be examples of such a drug. The L/T ratio indicates clearly how close an aerosol drug delivery system comes to the ideal of having all of the systemic drug exposure come from only the lung dose.

Pharmacodynamic Phase

KEY POINT

Pharmacodynamics describes the mechanism of activity by which drugs cause their effects in the body. The principal concept is the drug target protein (e.g., drug receptor).

The mechanism of drug action by which a drug molecule causes its effect in the body is the pharmacodynamic phase. Most drugs exert their effects by binding to protein targets and subsequently modulating the normal function of these proteins, usually inducing physiologic changes that affect multiple tissues and organ systems. The relevant protein targets include receptors, enzymes, ion channels, and carrier molecules. A **receptor** is any cell component that combines with a drug to change or enhance the function of the cell. In addition, some drugs exert their main therapeutic effect by interacting with DNA rather than by binding directly to proteins. The chemotherapeutic agent cisplatin inhibits cell division by binding to and disrupting cancer cell DNA, and the antiviral drug ganciclovir inhibits herpes virus replication by insinuating itself in the viral DNA and stopping further transcription.

Structure–Activity Relationships

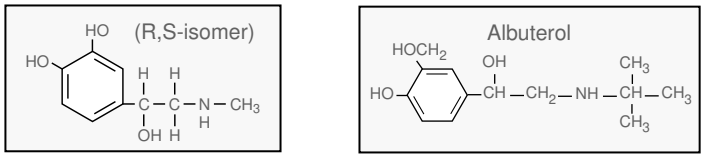
The matching of a drug molecule with a receptor or enzyme in the body is based on a structural similarity between the drug and its binding site. The relationship between the chemical structure of a drug and its clinical effect or activity is termed the **structure–activity relationship (SAR)**. Isoproterenol and albuterol are examples of two aerosol bronchodilators whose differing structures cause different pharmacokinetic activity and tissue responses.

The structures of isoproterenol and albuterol are illustrated in Fig. 2.8, with a summary of two critical differences in their pharmacokinetic profile and one critical difference in their side effects (heart rate increase). Although the two structures are very similar, and both are in the same family of β-adrenergic bronchodilators (see Chapter 6 for a discussion of this class of drugs), they are different. Isoproterenol is a catecholamine, which is metabolized rapidly because it is absorbed in the airway by the enzyme catechol *O*-methyltransferase (COMT), giving it a short duration of action. Albuterol, a saligenin, is not a substrate for the enzyme COMT but is, instead, metabolized through sulfate conjugation, a slower process. This difference is caused by the substitution of $HOCH_2$ for the OH group at the carbon-3 position. In addition, the structures of the two side chains are sufficiently different to change their receptor selectivity. Isoproterenol matches to receptors found in the airway (β_2 receptors) and the heart (β_1 receptors), whereas albuterol is more selective for receptors in the airway only. In recommended doses, albuterol has little or no effect on heart rate; however, isoproterenol usually causes an increase in heart rate.

Nature and Type of Drug Receptors

KEY POINT

Two mechanisms of drug–receptor action form the basis for the effects of two drug classes in respiratory care: intracellular receptor binding and modified gene transcription by lipid-soluble drugs (glucocorticoids) and receptors linked to their effector systems by G proteins (β-adrenergic bronchodilators).



Structure:	Catecholamine	Saligenin (Catecholamine analogue)
Pharmacokinetics:	Peak effect: 20 min Duration: 1.5–2 hr	Peak effect: 30–60 min Duration: 4–6 hr
Side effect:	Increased heart rate	Little/no change in heart rate
Class of drug:	Adrenergic bronchodilator	Adrenergic bronchodilator
Therapeutic effect:	Relax airway, smooth muscle	Relax airway, smooth muscle

• **Fig. 2.8** Structure–activity relationships (SARs) for two drugs representing the same class of bronchodilator. Racemic epinephrine and albuterol are both β-adrenergic agents, with minor structural differences leading to significantly different clinical effects.

At present, drugs having the greatest relevance to respiratory therapy act through receptor proteins, although enzymes are important targets for some antibiotics, antiviral drugs, and antihypertensive drugs. Receptors for many drugs have been biochemically purified and directly characterized, whereas in the past, such receptors were only indirectly inferred from drug action and differences of action between similar drugs.

Drug Receptors

Most drug receptors are proteins, or polypeptides, whose shape and electric charge provide a match to a drug's corresponding chemical shape or charge. Drug–receptor proteins include receptors on cell surfaces and within the cell.

The process by which attachment of a drug to its receptor results in a clinical response involves complex molecular mechanisms. This process sends a signal from the drug chemical into an intracellular sequence that controls cell function. Usually, the drug attaches to a receptor protein that spans the cell membrane, so the process is one of "transmembrane signaling."

Four mechanisms for transmembrane signaling are well understood. Each mechanism can transduce signals for a group of different drug receptors and for different drugs. The four mechanisms are as follows:

1. Lipid-soluble drugs cross the cell membrane and act on intracellular receptors to initiate the drug response. *Examples:* corticosteroids, vitamin D, thyroid hormone.
2. The drug attaches to the extracellular portion of a protein receptor, which projects into the cell cytoplasm (a "transmembrane protein") and activates an enzyme system, such as tyrosine kinase, in the intracellular portion to initiate an effect. *Examples:* insulin, platelet-derived growth factor (PDGF).
3. The drug attaches to a surface receptor that regulates the opening of an ion channel. *Examples:* acetylcholine receptors on skeletal muscle, γ-aminobutyric acid (GABA).
4. The drug attaches to a transmembrane receptor that is coupled to an intracellular enzyme by a G protein (guanine nucleotide–regulating protein). *Examples:* β-adrenergic agents, acetylcholine at parasympathetic nerve endings.

The first, third, and fourth mechanisms are reviewed in more detail in the following sections because these are the basis for the activity of drugs commonly used in respiratory care.

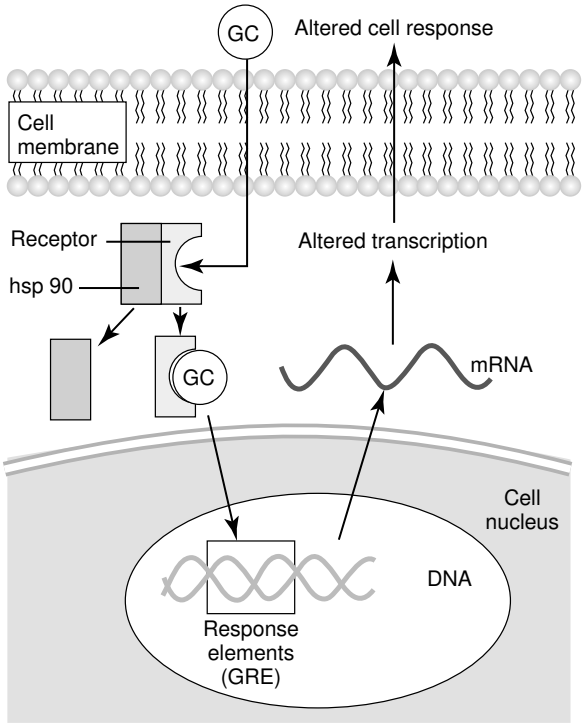
Lipid-Soluble Drugs and Intracellular Receptor Activation

Intracellular receptor activation by lipid-soluble drugs is the basis on which corticosteroids, an important class of drugs in respiratory care, cause a cell response. Examples of corticosteroid drugs are inhaled beclomethasone and flunisolide and oral prednisone. In this drug–receptor mechanism, the drug is sufficiently lipid soluble to cross the lipid bilayer of the cell membrane, diffuse into the cytoplasm, and attach to an intracellular polypeptide receptor. The drug–receptor complex translocates to the cell nucleus and binds to specific DNA sequences termed *hormone response elements,* which can either stimulate or repress the transcription of genes in the nucleus. An example of such drug-receptor signaling is given in Fig. 2.9, for glucocorticoid drugs, such as inhaled flunisolide or oral prednisone. The glucocorticoid diffuses across the cell membrane and attaches to a receptor in the cytoplasm. Attachment of the drug to the receptor causes displacement of certain proteins, termed *heat shock proteins,* and a change in the receptor configuration to an active state. The newly coupled drug–receptor complex moves or *translocates* to the nucleus of the cell, where it pairs with other drug–receptor complexes, which then bind to a glucocorticoid response element (GRE) of the cell's DNA. This binding initiates or represses cell response and transcription of target genes (see Chapter 11 for a discussion of the mechanism and effects of glucocorticoids).

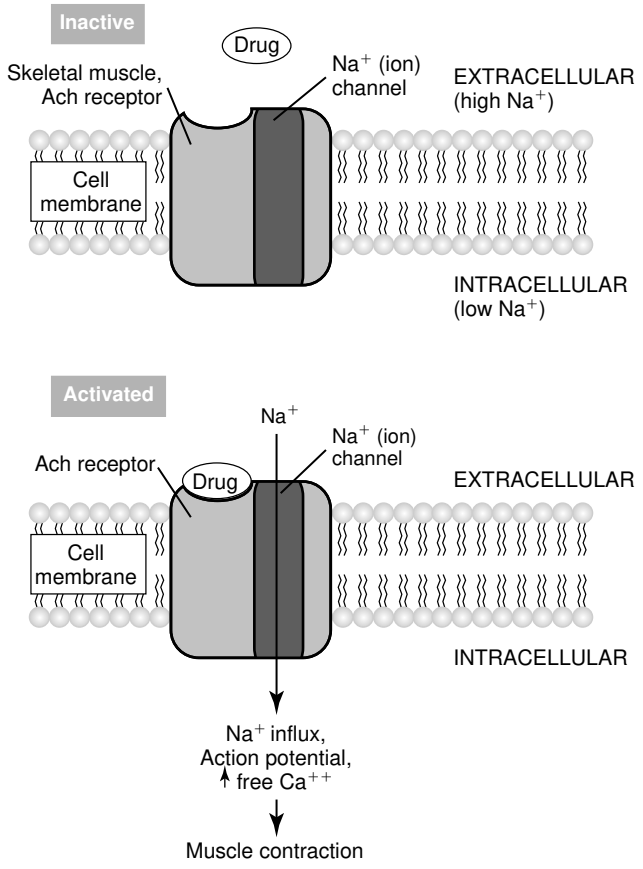
Drugs that act by diffusing into the cell and regulating gene responses have longer periods for observed responses, ranging from 30 minutes to several hours. Typically, there is also a persistence of effect for hours or days, even after the drug has been eliminated from the body.

Drug-Regulated Ion Channels

Another process of drug signal transduction regulates the flow of ions, such as sodium or potassium, through cell membrane channels. This has been depicted in Fig. 2.10. The drug binds to a receptor on the cell membrane surface. The receptor has a portion above or on the surface of the cell membrane and extends through the membrane into the cytoplasm of the cell. When activated by the drug (or by an endogenous ligand), the receptor opens an ion channel to allow increased transmembrane conductance of an ion. An example of such a receptor is that for acetylcholine, a neurotransmitter, on skeletal muscle. This acetylcholine receptor is termed



• **Fig. 2.9** Diagram of the mechanism of action for lipid-soluble drugs, such as glucocorticoids, which bind to intracellular receptors and then modify cell nuclear transcription. *GC,* Glucocorticoid; *GRE,* glucocorticoid response element; *hsp 90,* heat shock protein 90.



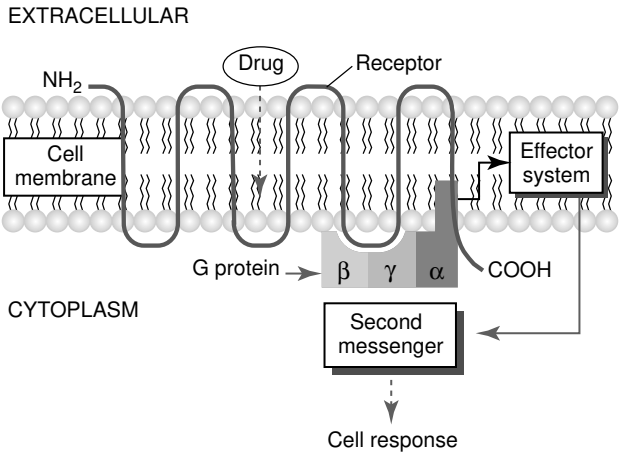
• **Fig. 2.10** Illustration of the drug signal mechanism that regulates ion channel flow to cause a drug response, such as that of acetylcholine *(Ach)* or nicotine in stimulating skeletal muscle fibers to contract.

a *nicotinic receptor* because it responds to the substance nicotine as well as acetylcholine. Attachment of acetylcholine or nicotine opens an ion channel and allows the high sodium (Na^+) concentration in extracellular fluid to flow into the lower concentration of the cell. This produces a reversal of voltage, or *depolarization,* and a corresponding muscle twitch. Acetylcholine is the neurotransmitter for voluntary muscle contraction and movement, and stimulation by nicotine can increase skeletal muscle tremor.

Receptors Linked to G Proteins

G protein–linked receptors mediate bronchodilation and bronchoconstriction in the airways in response to endogenous stimulation by the neurotransmitters epinephrine and acetylcholine. These same airway responses can be elicited by adrenergic bronchodilator drugs (discussed in Chapter 6) or blocked by acetylcholine-blocking (anticholinergic) agents, such as ipratropium bromide (discussed in Chapter 7). G proteins and G protein–linked receptors also mediate the effects of other chemicals, including the effects of histamine and glucagon, and the phototransduction of light in retinal rods and cones. Drug-receptor signaling with G protein–linked receptors involves three main components: the *drug receptor, G protein,* and *effector system.* When a drug attaches to a G protein–linked receptor, these three components interact to cause a cellular response to the drug. The effector system triggers the cell response by activating or inhibiting a *second messenger* within the cell. Fig. 2.11 shows the main elements of a G protein–linked receptor. Each of the major elements in this signaling mechanism complex is described briefly, along with the dynamics of their interaction.

Receptors that couple with G proteins have been well characterized and show a similar structure in which a polypeptide chain crosses the cell membrane seven times, giving a serpentine

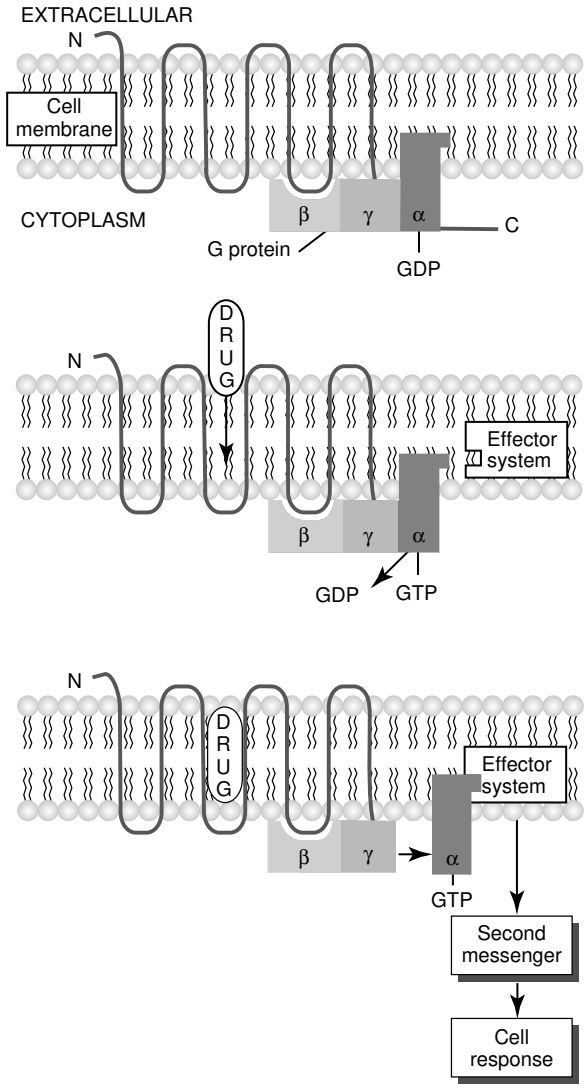


Example:	
Drug:	β-adrenergic bronchodilator
Receptor:	β-receptor
G Protein	Gs
Effector:	adenylyl cyclase
Second messenger:	cyclic 3',5',-AMP

• **Fig. 2.11** Simplified diagram of the components by which a G protein–linked receptor causes a cell response: drug, receptor, G protein, effector system, and second messenger. Each of these components is identified in this example of a β-adrenergic bronchodilator drug and the β receptor, which is a G protein–linked receptor. *Gs,* Stimulatory G protein.

appearance to the receptor. The polypeptide chain has an amino (NH_2, or N) terminal site outside the cell membrane and a carboxyl (COOH, or C) terminal inside the cell. Although the seven transmembrane segments of the receptor are depicted in Fig. 2.12 as being positioned side by side, the receptor appears to form a cylindrical structure if viewed perpendicular to the surface of the cell membrane, with the transmembrane loops forming the sides of the cylinder. The drug usually couples to the receptor at a site surrounded by the transmembrane regions of the receptor protein, that is, within the interior of the cylinder. The receptor activates a G protein on the cytoplasmic (inner) surface of the cell membrane. The site of the interaction of the G protein with the receptor polypeptide is thought to be at the third cytoplasmic loop of the receptor chain.

G proteins are so termed because they are a family of guanine nucleotide–binding proteins with a three-part, or *heterotrimeric,* structure. The three subunits of the G protein are designated by the Greek letters alpha (α), beta (β), and gamma (γ). The α subunit differentiates members of the G protein family. On the basis of the α subunit, the G protein is classified into subgroups, such as Gs, which *stimulates* an effector system, and Gi, which *inhibits* the effector system. Other types of G proteins have been identified as well; however, they are not reviewed in this chapter.



• **Fig. 2.12** Sequential diagram of G protein–linked receptor activation and G protein function in linking a drug signal to a cell response.

The activated G protein changes the activity of an *effector system,* which may be either an enzyme, which catalyzes the formation of a *second messenger,* or an ion channel, which allows the outflow of potassium (K^+) ions from the cell. One of the second messengers is the well-known cyclic adenosine 3′,5′-monophosphate (cAMP). The effector enzyme for increasing cAMP is adenylyl cyclase (previously termed adenyl cyclase), which converts adenosine triphosphate (ATP) to cAMP. The G protein that stimulates adenylyl cyclase is the Gs (for *stimulatory*) protein. β receptors, which couple with β-adrenergic bronchodilators, activate Gs proteins. Another G protein, Gi (for *inhibitory*), inhibits the activation of adenylyl cyclase; Gi proteins are activated by cholinergic (muscarinic) agonists, such as acetylcholine or the drug methacholine.

The dynamics of cell signaling by G protein–linked receptors are illustrated schematically in Fig. 2.12. When there is no drug attached to the receptor site, the α subunit of the G protein is bound to guanosine diphosphate (GDP), and the G protein is in an inactive state. When a drug attaches to the receptor, there is a change in the receptor conformation that causes the release of GDP and the binding of guanosine triphosphate (GTP) to the α subunit. This is the active state for the G protein. The GTP-bound α subunit dissociates, or *unlinks,* from the β-γ portion and couples with the effector system to stimulate or inhibit a second messenger within the cell. The GTP bound to the α subunit is hydrolyzed by a guanosine triphosphatase (GTPase) enzyme, dissociates from the effector, and reassociates with the β-γ dimer. The G protein–linked receptor is then ready for reactivation.

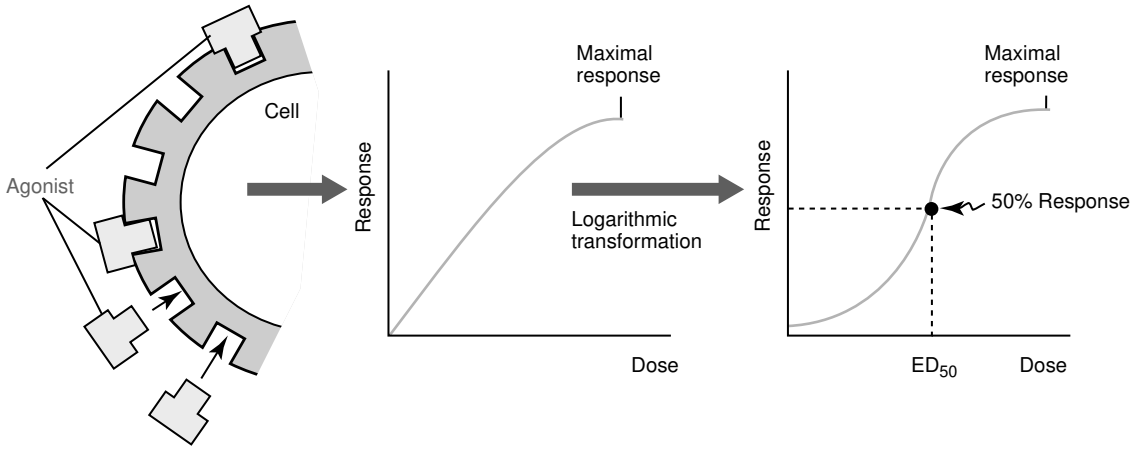
Details on specific G proteins, their effector systems, and their second messengers are presented for neurotransmitters, such as epinephrine and acetylcholine in the nervous system (see Chapter 5), and for the classes of drugs that link to such receptors, such as adrenergic bronchodilators (see Chapter 6) and anticholinergic bronchodilators (see Chapter 7).

Dose–Response Relationships

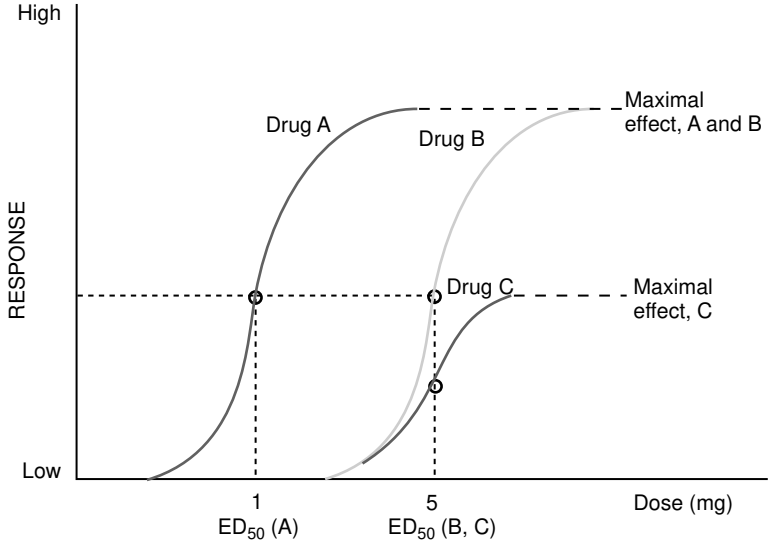
KEY POINT

Various terms describe the dose–response relationship of drugs, while they combine with their corresponding receptors, and drug interactions: *potency*; *maximal effect*; *therapeutic index (TI)*; *agonists* and *antagonists*; *synergism*; *additivity*; *potentiation*; and reaction types, such as *idiosyncracy*, *hypersensitivity*, *tolerance*, and *tachyphylaxis.*

The response to a drug is proportional to the drug's concentration. As drug concentration increases, the number of receptors occupied increases, and the drug effect also increases up to a maximal point; this is graphed as a dose–response, or concentration–effect, curve (Fig. 2.13). Increasing amounts of a drug increase the response in a fairly direct fashion; however, the rate of response usually diminishes as the dose increases until a plateau of maximal effect is reached. Such a convex, or *hyperbolic,* curve is normally transformed mathematically by using the logarithm of the dose so that a sigmoid curve is obtained. The linear midportion of a sigmoid curve allows for easier comparison of the dose–response curve for different drugs. In particular, the dose at which 50% of the response to the drug occurs is indicated in Fig. 2.13 and is referred to as the ED_{50}, the dose of drug that produces 50% of the maximal effect. This value may also be denoted as the EC_{50}, for effective concentration giving 50% of maximal response.



• **Fig. 2.13** Illustration of the dose-response curve *(left),* showing an increasing effect that ultimately plateaus, and its logarithmic transformation to produce a sigmoid curve *(right).* ED_{50}, Drug dose that produces 50% of the maximal effect.



• **Fig. 2.14** The potency of a drug is defined as the dose producing 50% of the drug's maximal effect. Drug *A* is more potent than drug *B;* however, drugs *B* and *C* are equally potent, although drug *C* has less maximal effect than drug *B.*

Potency versus Maximal Effect

Dose–response curves are the basis for defining and illustrating several concepts used to characterize and compare drugs. Two concepts that allow comparison of drugs are potency and maximal effect, both illustrated in Fig. 2.14.

1. *Potency:* Refers to the concentration (EC_{50}) or dose (ED_{50}) of a drug producing 50% of the *maximal response* of the drug. The potency of two drugs, *A* and *B,* can be compared on the basis of the ED_{50} values of the two drugs: relative potency, A and B = ED_{50} (B)/ED_{50} (A).
2. *Maximal effect:* The greatest response that can be produced by a drug, a dose above which no further response can be elicited.

The lower the ED_{50} for a given drug, the more potent is the drug, as shown in Fig. 2.14. Curves for drugs *A* and *B* show different potencies. If the ED_{50} for drug *B* is 5 mg and for drug *A* is 1 mg, then drug *A* is five times more potent than drug *B:*

$$ED_{50}(B)/ED_{50}(A) = 5\ mg/1\ mg = 5$$

Drug *B* requires five times the amount of drug *A* to produce 50% of its maximal effect. Potency is not the same as maximal effect, also illustrated in Fig. 2.14. *Potency* is relatively defined by using the ED_{50} values of two drugs, whereas *maximal effect* is absolutely defined as a physiologic or clinical response. The curves indicate that drugs *B* and *C* have the same potency; that is, the same dose produces 50% of the maximal response. However, drug *B* has a greater maximal effect compared with drug *C.* Because the ED_{50} is the dose causing a response that is half the maximal response of the *same* drug, two drugs can have different maximal responses but the same ED_{50} (and the same potency), as shown in Fig. 2.14.

Therapeutic Index

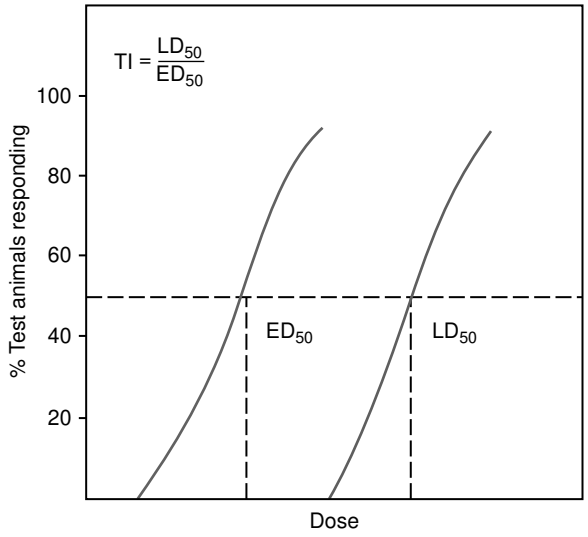
The **therapeutic index (TI)** can be defined as the ratio of the lethal dose for 50% of the test population (LD_{50}) to the ED_{50} for a given drug, with ED_{50} and LD_{50} indicating half of the test subjects, rather than a 50% clinical response. The TI is also based on the dose–response curve of a drug. However, instead of a graded

clinical or physiologic response, such as an increase in heart rate, we substitute an all-or-nothing response of improvement for each subject, or toxicity or death for each subject. In this case the ED_{50} represents the dose of the drug at which half of the test subjects improve. Similarly, the LD_{50} is the lethal dose for 50% of the test population. Doses are established for a test population of animals (as illustrated in Fig. 2.15).

The ratio of the dose that is toxic to 50% of test subjects to the dose that provides relief to 50% of the subjects is the clinical TI. This index represents the safety margin of the drug. The smaller the TI, the greater is the possibility of crossing from a therapeutic effect to a toxic effect. Theophylline is a drug used in respiratory care that has a narrow therapeutic margin. As a result, toxic side effects can be seen at close to therapeutic dose levels in some individuals.

Agonists and Antagonists

An **agonist** is a drug or chemical that binds to a corresponding receptor (has affinity) and *initiates* a cellular effect or response (has efficacy). An **antagonist** is a drug or chemical that is able to bind to a receptor (has affinity) but causes no response (zero efficacy). Because the antagonist drug is occupying the receptor site, it can prevent other drugs or an endogenous chemical from reaching and activating the receptor site. By doing so, an antagonist *inhibits* or *blocks* the agonist at the receptor. Agonists are divided further into *full* and *partial agonists.* A full agonist is a drug that gives a higher maximal response than a partial agonist. The dose–response curves for a partial agonist and a full agonist are represented in Fig. 2.16. Both have receptor affinity, but a partial agonist has less efficacy than a full agonist.



• **Fig. 2.15** Therapeutic index *(TI),* defined as the ratio of the dose that is lethal for 50% of test animals *(LD_{50})* to the dose causing improvement in 50% of test animals *(ED_{50}).*

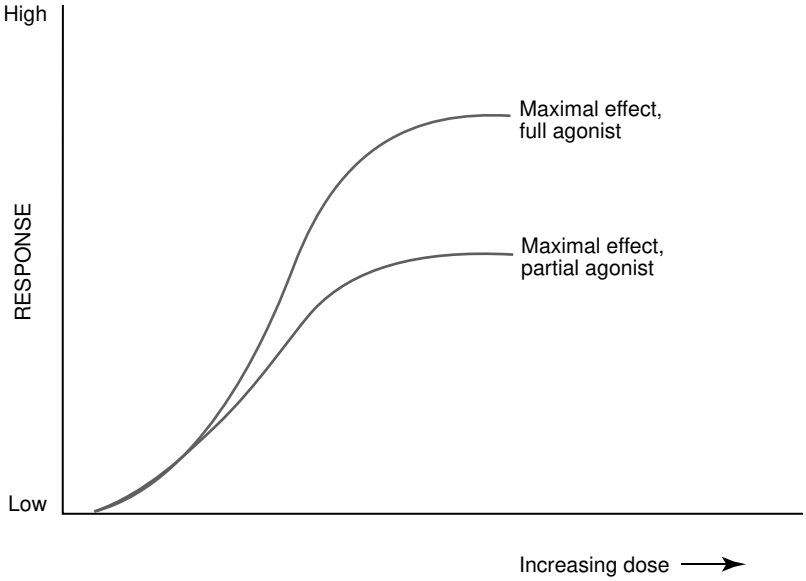
Drug Interactions

The concept of drug antagonism just discussed is an example of a drug interaction in which one drug can block the effect of another. Mechanisms of drug antagonism are as follows:

- *Chemical antagonism:* Direct chemical interaction between a drug and the biologic mediator that inactivates the drug. An example is chelation of toxic metals by a chelating agent.
- *Functional antagonism:* Can occur when two drugs each produce an effect and the two effects cancel each other. For example, methacholine can stimulate parasympathetic (muscarinic) receptors in the airways, causing bronchoconstriction; epinephrine can stimulate β_2 receptors in the airways, causing bronchodilation.
- *Competitive antagonism:* Occurs when a drug has affinity for a receptor but no efficacy and at the same time blocks the active agonist from binding to and stimulating the receptor. For example, fexofenadine is a competitive antagonist to histamine on specific receptors (H_1) on bronchial smooth muscle and the nasopharynx and is used to treat allergies to pollens.

The following terms are used to describe positive interactions between two drugs:

- *Synergism:* Occurs when two drugs act on a target organ by different mechanisms of action, and the effect of the drug pair is greater than the sum of the separate effects of the drugs.
- *Additivity:* Occurs when two drugs act on the same receptors, and the combined effect is the simple linear sum of the effects of the two drugs, up to a maximal effect.
- *Potentiation:* A special case of synergism in which one drug has no effect but can increase the activity of the other drug.



• **Fig. 2.16** Dose–response curves for full and partial agonists, illustrating the greater maximal effect of the full agonist.

Terms for Drug Responsiveness

Individuals exhibit variation in their responses to drugs; the dose–response curves previously illustrated represent an average of an entire group. The following terms are encountered in pharmacology to describe individual reactions to drugs:

- ***Idiosyncratic effect:*** Effect that is the opposite of, or unusual, or an absence of effect, compared with the predicted usual effect in an individual.
- ***Hypersensitivity:*** Allergic or immune-mediated reaction to a drug, which can be serious, requiring airway maintenance or ventilatory assistance.
- ***Tolerance:*** Decreasing intensity of response to a drug over time.
- ***Tachyphylaxis:*** Rapid decrease in responsiveness to a drug.

Pharmacogenetics

KEY POINT

Pharmacogenetics refers to hereditary differences in the way the body handles specific drugs.

The well-described variations among patients in responses to drugs are being increasingly traced to hereditary differences. The study of these hereditary or genetic differences is referred to as **pharmacogenetics**. These genetic variations may not be manifested as an "abnormality" until the patient is challenged with a drug, at which time the irregularity in the pharmacokinetic or pharmacodynamic response is revealed. Genetic differences affecting drug metabolism have been most extensively studied, although variation in target proteins may be equally important.

Several examples can be given from drugs commonly seen in respiratory and critical care:

- *Isoniazid:* Antituberculosis drug whose rates of metabolism and inactivation vary among individuals, with evidence of rapid and slow inactivators. The proportion of rapid versus slow inactivators is about 50/50 among white and black individuals, but Inuit and some Asian people tend to be rapid inactivators.
- *Succinylcholine:* Neuromuscular paralyzing agent used during surgery. Succinylcholine is normally metabolized by a butyrylcholinesterase enzyme (pseudocholinesterase). Approximately 1 in 3000 individuals has a genetically determined variant of this enzyme. As a result, a patient may take several hours to recover from the drug, rather than the several minutes usually seen, and may also begin to breathe spontaneously. Mechanical ventilatory support would be required until spontaneous breathing is adequate.
- *Isoflurane:* Inhalation anesthetic that (similar to several other related anesthetics) can cause malignant hyperthermia in genetically susceptible individuals. Patients with an atypical variant of a calcium release channel can die as a result of this serious complication of general anesthesia, which involves a rapid increase in body temperature and increased oxygen consumption.

SELF-ASSESSMENT QUESTIONS

Answers can be found in Appendix A.

1. If a drug is in liquid solution, what routes of administration are available for its delivery, considering only its dosage form?
2. Although generic drug equivalents all have the same amount of active drug, do formulations of the same drug from different manufacturers all have the same ingredients?
3. If 200 mg of a drug results in a plasma concentration of 10 mg/L, what is the calculated volume of distribution (V_D)?
4. If the V_D of a drug, such as phenobarbital, is 38 L/70 kg, and an effective concentration is 10 mg/L, what loading dose would be needed for an average adult (assuming total bioavailability)?
5. If an inhaled aerosol has zero gastrointestinal absorption of an active drug and only lung absorption, what is the L/T ratio?
6. True or False: A patient uses a reservoir device with an inhaled aerosol, and there is no swallowed portion of the drug; therefore there are no systemic side effects.
7. Which receptor system signal mechanism is responsible for the effects caused by β-receptor activation, such as those seen with adrenergic bronchodilators (e.g., albuterol)?

CLINICAL SCENARIO

Answers can be found in Appendix A.

A resident orders racemic epinephrine, a bronchodilator, to be given qid to a 67-year-old man. The patient has had chronic obstructive pulmonary disease (COPD) for the past 10 years and was admitted to the hospital the previous evening with a respiratory infection. At 8:00 AM, you administer the prescribed usual recommended dose of aerosol treatment via a nebulizer. After the treatment, the patient's respiratory rate is reduced from 26 breaths/min to 18 breaths/min, and there is less use of accessory muscles. Wheezing on auscultation is also decreased, although you hear adequate breath sounds bilaterally. He seems less short of breath. At 10:00 AM, he is exhibiting moderate respiratory distress, using accessory muscles, complaining of dyspnea, and having increased wheezing on auscultation. His next aerosol treatment is due at noon. He admits to no chest pain; wheezes and breath sounds can be auscultated over the entire thorax. You review the pharmacokinetics of racemic epinephrine and find the following:

- *Onset:* 3 to 5 minutes
- *Peak effect:* Approximately 15 minutes
- *Duration:* Approximately 2 hours or less

Using the SOAP (subjective, objective, assessment, and plan) method, assess this clinical scenario.

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3

Administration of Aerosolized Agents

DOUGLAS S. GARDENHIRE

CHAPTER OUTLINE

OBJECTIVES

After reading this chapter, the reader will be able to:

1. Define terms that pertain to administration of aerosol agents
2. Define *aerosol therapy*
3. Select an appropriate aerosol medication nebulizer on the basis of particle size distributions
4. Discuss aerosol particle size and deposition in the lungs
5. Differentiate between the types of aerosol devices
6. Describe the clinical applications of aerosol devices
7. Recommend the use of various aerosol devices

KEY TERMS AND DEFINITIONS

Aerodynamic diameter of a particle Diameter of a unit-density (1 g/cc) spherical particle having the same terminal settling velocity as the measured particle.

Aerosol Suspension of liquid or solid particles 0.001 to 100 micrometers (μm) in diameter in a carrier gas.

Aerosol therapy Delivery of aerosol particles to the lungs.

Cascade impactor Device that uses multiple steps in determining size of aerosol particles.

Chlorofluorocarbon (CFC) Liquefied gas (e.g., Freon) propellant used to administer medication from a metered dose inhaler (MDI).

Dead volume Amount of solution that remains in the reservoir of a small volume nebulizer once sputtering begins, causing a decrease in aerosolization.

Deposition Process of particles depositing out of suspension to remain in the lung.

Continued

Heterodisperse In reference to the size of particles in an aerosol, meaning the particles are of different sizes.
Hydrofluoroalkane (HFA) Nontoxic liquefied gas propellant used to administer medication from an MDI.
In vitro Mechanically simulating the clinical setting; testing in a laboratory.
In vivo Testing done on animals or humans; clinical testing.
Monodisperse In reference to the size of particles in an aerosol, meaning all particles being the same size.
Nebulizer Device used for making a fine spray or mist, also known as an *aerosol generator*.
Penetration Refers to the depth within the lung reached by particles.
Polydisperse In reference to the size of particles in an aerosol, meaning many different particle sizes.
Reservoir device Global term describing or referring to extension, auxiliary, or add-on devices attached to MDIs for administration. This term can include "spacer" and "valved holding chamber" (defined subsequently).
Spacer Simple tube or extension device with no one-way valves to contain the aerosol cloud; its purpose is simply to extend the MDI spray away from the mouth.
Stability Describing the tendency of aerosol particles to remain in suspension.
Valved holding chamber Spacer device with the addition of a one-way valve to contain and hold the aerosol cloud until inspiration occurs.

Aerosol therapy refers to the delivery of aerosol particles to the respiratory tract. At the present time, there are three main uses of aerosol therapy in respiratory care:

1. Humidification of dry inspired gases by using bland aerosols
2. Improved mobilization and clearance of respiratory secretions, including sputum induction, by using bland aerosols of water and hypertonic or hypotonic saline
3. Delivery of aerosolized drugs to the respiratory tract

This chapter presents information on delivery of aerosolized drugs to the respiratory tract. As outlined in Chapter 2, the first prerequisite for a drug to exert a therapeutic effect at the target organ is an effective dosage form and route of administration for the target organ. Aerosol generation and delivery to the lung is a complex topic. Development of the technology and the scientific basis of inhaled aerosol administration is ongoing. This chapter reviews physical principles of aerosol delivery to the airways and aerosol-generating devices for inhalation of drugs. Research findings on aerosol delivery devices and methods of administration are summarized. The general advantages supporting the use of aerosolized drug therapy in respiratory care and the disadvantages with this method of drug delivery are summarized in Box 3.1.

• BOX 3.1 Advantages and Disadvantages Seen With Aerosol Delivery of Drugs

Advantages
- Aerosol doses are smaller than doses for systemic treatment.
- Onset of drug action is rapid.
- Drug delivery is targeted to the respiratory system for local pulmonary effect.
- Systemic side effects are fewer and less severe than with oral or parenteral therapy.
- Inhaled drug therapy is painless and relatively convenient.
- The lung provides a portal to the body for inhaled aerosol agents intended for systemic effect (e.g., pain control, insulin).

Disadvantages
- Numerous variables affect dose of aerosol drug delivered to airways.
- Dose estimation and dose reproducibility are inconsistent.
- Many patients have difficulty in coordinating hand action and breathing with metered dose inhalers (MDIs).
- Many physicians, nurses, and therapists lack knowledge of device use and administration protocols.
- Standardized technical information on aerosol-producing devices is lacking for practitioners and patients.
- Numerous device types and variability of use are confusing to patients and practitioners.

Physical Principles of Inhaled Aerosol Drugs

KEY POINT

An *aerosol* is a suspension of solid or liquid particles whose *deposition* in the respiratory tract is determined by *inertial impaction, gravitational settling (sedimentation),* and, perhaps less importantly, *diffusion (brownian motion).*

The term *aerosol* has been used since the beginning of the twentieth century; however, inhaled agents used for medicinal purposes date back 4000 years ago.[1] The following definitions apply to inhaled therapeutic aerosols:

Aerosol: Suspension of liquid or solid particles between 0.001 and 100 micrometers (μm) in diameter in a carrier gas.[2] For pulmonary diagnostic and therapeutic applications, the particle size range of interest is 1 to 10 μm. Particles in this size range are small enough to exist as a suspension and to enter the lung and large enough to deposit and contain the required amount of an agent.[3,4]

Stability: Describing the tendency of aerosol particles to remain in suspension.

Penetration: Referring to the depth within the lung reached by particles.

Deposition: Describing the process by which particles deposit out of suspension to remain in the lung.

Aerosol-generating devices for orally inhaled drugs have typically had an efficiency of 10% to 15%; that is, only 10% to 15% of a given dose from a device usually reaches the lower respiratory tract, regardless of the device type. Newer aerosol-generating devices are proving to be exceptions to this lack of efficiency, with 30% to 50% or more of the dose reaching the lungs.

Aerosol Particle Size Distributions

KEY POINT

A major factor in lung penetration by aerosols is particle size, which is best characterized by the *mass median aerodynamic diameter (MMAD)* for inhaled drugs because particle mass is a function of the third power of the particle radius. The particle size of interest for pulmonary applications is in the range of 1 to 10 μm, and the fine particle fraction (FPF) is considered to include particles less than 5 μm in size.

Aerosol particles produced for inhalation into the lungs via inhalant devices, such as metered dose inhalers (MDIs), small volume nebulizers (SVNs), and dry powder inhalers (DPIs), include a range of sizes (**polydisperse** or **heterodisperse**) rather than a single size (**monodisperse**).

Count mode: Most frequently occurring particle size in the distribution.

Count median diameter (CMD): Particle size above and below which 50% of the particles are found (i.e., the size that evenly divides the number of particles in the distribution).

Mass median diameter (MMD) or MMAD: Particle size above and below which 50% of the mass of the particles are found (i.e., the size that evenly divides the mass of the particles in the distribution).

Geometric standard deviation (GSD): Measure of the dispersion of a distribution (i.e., the scattering of values from the average), calculated as the ratio of particle size below which 84% of the particles occur to the particle size below which 50% occur, in a log-normal distribution. This ratio determines how spread out the particles are in relationship to their size.

The MMD, or MMAD, indicates where the mass of drug is centered in a distribution of particle sizes. Aerosol particles are three-dimensional and have volume. Aerosol particles are assumed to be roughly spherical, and the relationship of volume (or mass, if all particles have equal densities) to diameter in a sphere is given by the following formula:

$$V = \left(\frac{4}{3}\right)\pi r^3$$

V = volume; r = radius

The volume increases or decreases as the third power of the radius of the particle, as seen in the preceding formula. As a result, the bulk of drug mass is centered in the larger particle sizes. Because it is the mass of the drug entering the lung on which the therapeutic effect is based, it is necessary to know where the mass is centered in a range of particle sizes to know whether that distribution will be efficient for penetration into the respiratory tract and delivery of an adequate dose.

EXAMPLE

Two hypothetical SVNs, *A* and *B,* have the following specifications from the manufacturer:

A	B
CMD = 1.9 μm	CMD = 1.7 μm
MMAD = 3.4 μm	MMAD = 7.9 μm
GSD = 1.2	GSD = 1.6

Although nebulizer *B* has a smaller CMD compared with nebulizer *A,* which appears to indicate that it gives smaller particles, it is evident from the respective MMADs that nebulizer *B* has more particles in a larger size range (≥5 μm) compared with nebulizer *A.* Nebulizer *A* produces particles whose mass centers within a lower size range (1–5 μm) and would be the better nebulizer for treatment of the lower respiratory tract.

Inspect aerosol products for their MMAD because this is the best way to determine whether the nebulizer would be better suited for the upper or lower airway.

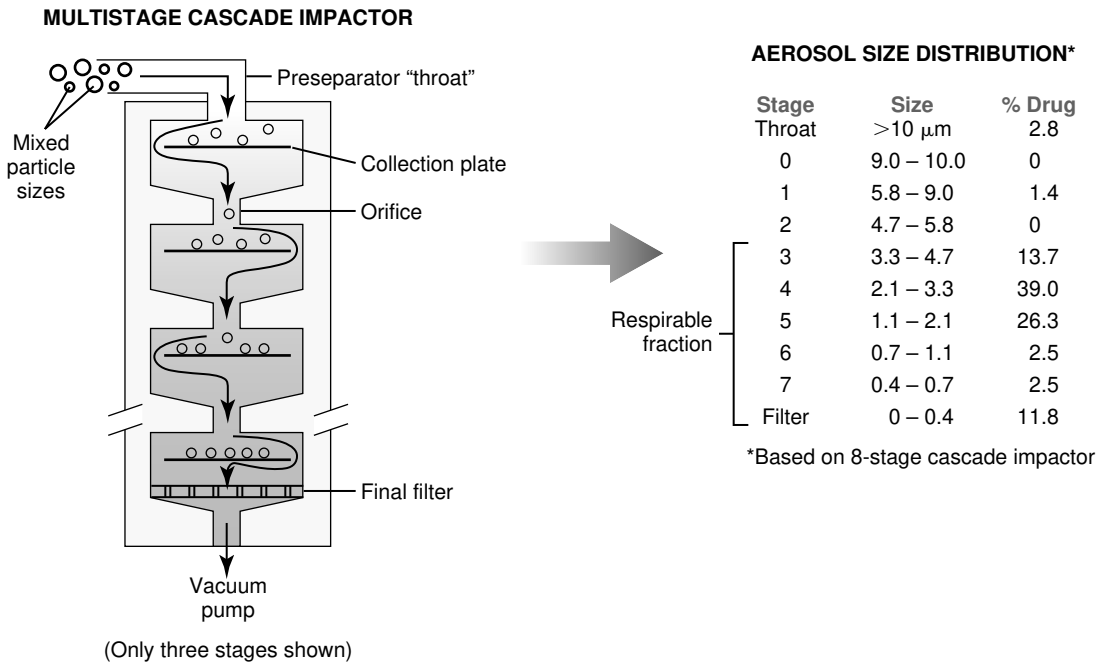
Aerosol generators should be characterized by using the MMD for the center of distribution and either the standard deviation or GSD to indicate the range of variability of particle size.

Measurement of Particle Size Distributions

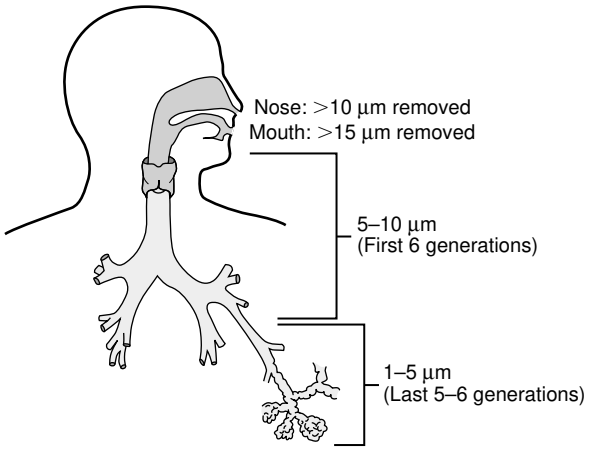
Several physical methods are used to measure aerosol particle size distributions, including *cascade impaction* and, less commonly, *laser scattering.* The **cascade impactor** measures what is termed the *aerodynamic diameter of aerosols* because the measurement is based on the aerodynamic behavior (sedimentation velocity and impaction characteristics) of the particles in the cascade impactor. Measuring particle size with the *laser-scattering method,* the instrument determines the relationship between the intensity and the angle of light scattered from a particle, then calculates the particle size based on the Mie-scattering theory. The **aerodynamic diameter of a particle** is the diameter of a unit-density (1 g/cc) spherical particle having the same terminal settling velocity as the measured particle.[4,5]

The principle by which a cascade impactor measures the particle size distribution of an aerosol cloud is illustrated in a simplified diagram in Fig. 3.1. The *cascade impactor* consists of a series of stages, each of which has progressively smaller orifices through which the aerosol particles must pass. A constant flow draws the particles through the stages. The largest particles are collected on the first stage, and particles not impacting out at this stage move on to the subsequent stages with smaller orifices in the airstream. By means of successively smaller filtration stages, the particles are separated, or *fractionated,* on the basis of size. Any particles leaving the last stage are collected on a final filter.

The amount of aerosol on each stage is measured by weight or, preferably, by spectrophotometry or high-performance liquid chromatography (HPLC). HPLC is considered the most sensitive technique for quantifying the amount of aerosol on each stage. Because each stage is calibrated for a unit-density sphere of specific diameter, the distribution of aerodynamic diameters can be calculated as the percentage of a drug on each stage. The MMAD can be determined as the particle size dividing the drug in half. Sources of error in aerodynamic measures include particle bounce, interstage impaction, possible fragmentation of particles, and particle evaporation or condensation.[5] In addition, **in vitro** methods (mechanically simulating the clinical setting within a laboratory) of aerosol measurement may not reflect conditions in the human lung, such as temperature, humidity, inspiratory flow rates, and exhalation phase. Dolovich[6] reviewed in vitro measures used with MDI and auxiliary devices. Feddah et al.[7] found that MDI formulations did better in vitro compared with DPI formulations with respect to inhaled doses. The same method of aerosol characterization is not useful or accurate for different methods of aerosol production because of differences in the physical nature of their generation.



• **Fig. 3.1** The principle of aerodynamic particle size measurement, using multistage cascade impaction. A series of successively smaller orifices and collection plates separate large and smaller particle sizes. Drug amounts *(% Drug)* shown are actual measures of particle sizes for a sample of albuterol (Ventolin) through a Volumatic reservoir. (Data courtesy J. P. Mitchell, Trudell Medical International Aerosol Laboratory, London, Ontario, Canada.)



• **Fig. 3.2** Effect of aerosol particle size on area of preferential deposition within the airway.

To determine aerosol particle behavior in animals or humans, in vivo methods would be studied.

Particle Size and Lung Deposition

A major factor influencing aerosol deposition in the lung is particle size. The effect of particle size on deposition in the respiratory tract is illustrated in Fig. 3.2.

The upper airway (nose and mouth) is efficient in filtering particulate matter, so generally, there is 100% deposition in the nose and mouth of particles larger than 10 to 15 μm. Particles sized from 5 to 10 μm tend to deposit out in the upper airways and the early airway generations, whereas particles from 1 to 5 μm in size have a greater probability of reaching the lower respiratory tract (from the trachea to the lung periphery). Larger or coarser aerosol particles (≥5 μm in diameter) may be useful for treating the upper airway (nasopharynx and oropharynx). It is impossible to specify exactly where a given size of particle will deposit in the lung. Particle deposition is a function of several mechanisms, including the breathing pattern. For example, tables are often created listing the percentage of droplets of a given size that will deposit in the lung at each bronchial level.[8] Hoffman[9] observed that optimal deposition in the normal human lung is achieved for particles of 3 μm inhaled with low inspiratory flows of less than 1 L/sec (≤60 L/min) and tidal volumes of 1 L; total lung deposition is divided almost equally throughout the 23 lung generations.

Fine Particle Fraction

The labels *respirable fraction* and *respirable dose* were used previously to refer to the percentage or fraction of aerosol drug mass in a particle size range with a high probability of penetrating into the lower respiratory tract. These generally have been considered to be in the particle size range of less than 5 to 6 μm. There is rarely an absolute correspondence of lower respiratory tract deposition to this particle size range because of age, disease, and breathing patterns, all of which can affect lung deposition. The more descriptive terms *fine particle fraction (FPF)* and *fine particle dose (FPD)* were proposed for use in place of respirable fraction and respirable dose.[10] There was no consensus regarding what size fraction represents the FPF. These terms may be restricted to particles 1 to 3 μm, rather than particles less than 5 to 6 μm.

Particle Size and Therapeutic Effect

Because the respiratory tract apparently functions as a progressive filter of successively smaller particles from the upper airway to the periphery, specific areas of the respiratory tract may be targeted by various aerosol particle sizes. On the basis of the preceding considerations, the respiratory tract might be segmented according to particle size ranges, as discussed below.

Particles greater than 10 μm. Particles that are greater than 10 μm are useful to treat the nasopharyngeal and oropharyngeal regions. An example is a nasal spray for perennial rhinitis, such as a corticosteroid.

Particles 5 to 10 μm. Particles 5 to 10 μm may shift deposition to the more central airways, although significant oropharyngeal deposition is expected. An example is a nasal spray, but there is no one standard device that creates this specific particle size. Most aerosol devices use a smaller particle size (discussed below).

Particles 2 to 5 μm. As particle size decreases to less than 5 μm, deposition shifts from the oropharynx and large airways to the overall lower respiratory tract (large airways to periphery).[11] This size range is considered useful for the bronchoactive aerosols currently in use. For example, β-adrenergic receptors have been identified throughout the airway, but with greater density in bronchioles. Clay et al.[12] showed greater improvement in mid-maximal expiratory flow rates among patients using a β-adrenergic bronchodilator with an MMAD of 1.8 μm than with an MMAD of 4.6 or 10.3 μm. This finding was confirmed subsequently by Johnson et al.,[13] who found a greater response to the β-adrenergic bronchodilator albuterol (see Chapter 6) with an MMD of 3.3 μm compared with 7.7 μm. Leach[14] found similar results with a **chlorofluorocarbon (CFC)**-MDI of albuterol, where particles averaged 3.5 to 4.0 μm; however, when testing a **hydrofluoroalkane (HFA)**-MDI, particle size decreased to an average of 1.1 μm. In contrast, cholinergic receptors are numerous in proximal bronchial smooth muscle but rare in distal bronchioles.[15]

Particles 0.8 to 3.0 μm. Increased delivery of an aerosol to the lung parenchyma, including the terminal airways and alveolar region, can be achieved with particles less than 3 μm.[11] An MMAD of 1 to 2 μm is suggested for peripheral deposition of the antiinfective drug pentamidine to minimize deposition in and irritation of larger airways and to maximize intraalveolar deposition.[16] However, with the introduction of HFA-MDIs, a finer particle size is seen.[14]

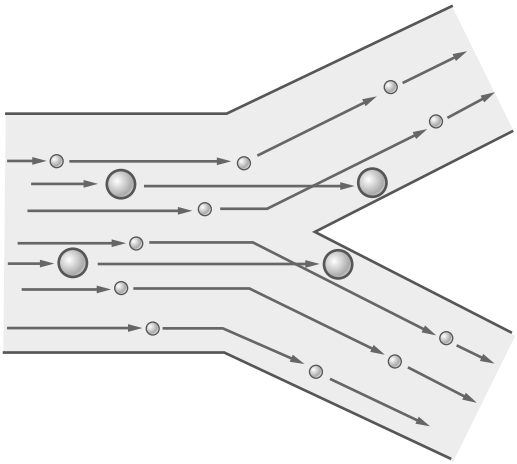
Mechanisms of Deposition

Three physical mechanisms usually are considered for aerosol particle deposition in the human lung:

1. Inertial impaction
2. Gravitational settling (sedimentation)
3. Diffusion (brownian motion).

Inertial Impaction. As shown in Fig. 3.3, *inertial impaction* is a function of particle size (mass) and velocity and increases with larger size and higher velocities. In the upper airway and early bronchial generations, particle velocity is highest, airflow tends to be turbulent, and total cross-sectional area of the airway is smallest. These factors favor inertial impaction for larger, fast-moving particles on the airway wall, especially at airway bifurcations. Deposition by inertial impaction is expected to occur in the first 10 airway generations.[4]

Gravitational Settling. *Gravitational settling,* or *sedimentation,* is a function of particle size and time. Settling is greater for larger particles with slow velocities, which are under the influence of gravity. As particles small enough to escape inertial impaction in earlier airway generations reach the periphery, velocity probably slows, and airflow is less turbulent. There is also a shorter distance to the airway wall in smaller, peripheral airways, favoring impaction resulting from settling (Fig. 3.4). The probability of deposition by sedimentation is highest in the last five or six airway generations.[4] Because the process of sedimentation is time dependent, the end-inspiratory breath hold should maximize deposition in the periphery. The rate of settling is proportional to the square of the particle size. For a 5-μm–diameter particle, the settling rate is reported to be 0.7 mm/sec.[17] The use of a breath hold can increase settling of particles; however, depending on particle size, a particle may not fall out of suspension.



• **Fig. 3.3** Inertial impaction of large particles, the masses of which tend to maintain their motion in straight lines. As airway direction changes, the particles are deposited on nearby walls. Smaller particles are carried around corners by the airstream and fall out less readily. (From Kacmarek, R. M., Stoller, J. K., & Heuer, A. J. (2017). *Egan's Fundamentals of Respiratory Care* (11th ed.). St. Louis, Missouri O: Mosby.)

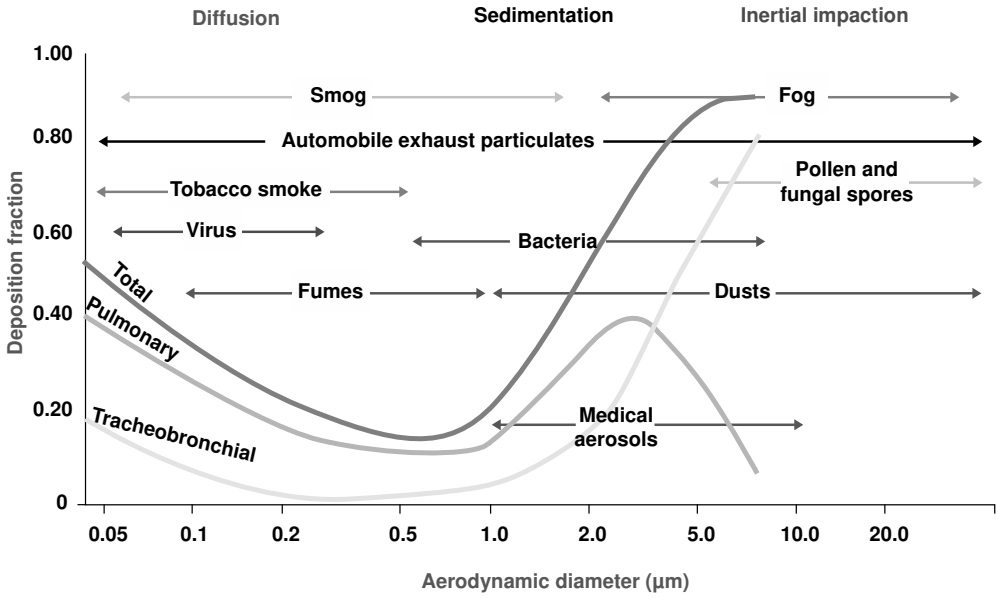
Diffusion (Brownian Motion). *Diffusion (brownian motion)* affects particles less than 1 μm in diameter and is a function of time and random molecular motion. Particles 0.1 to 1.0 μm in size may remain suspended or even exhaled because the time required to diffuse to the airway surface tends to be greater than the inspiratory time of a normal breath.[18] The importance of diffusion for lung deposition of therapeutic aerosols is debatable because the size range involved contains very little drug mass but gives great stability. Fig. 3.5 shows the relationship between particle size and aerosol deposition in the respiratory tract.

CLINICAL CONNECTION

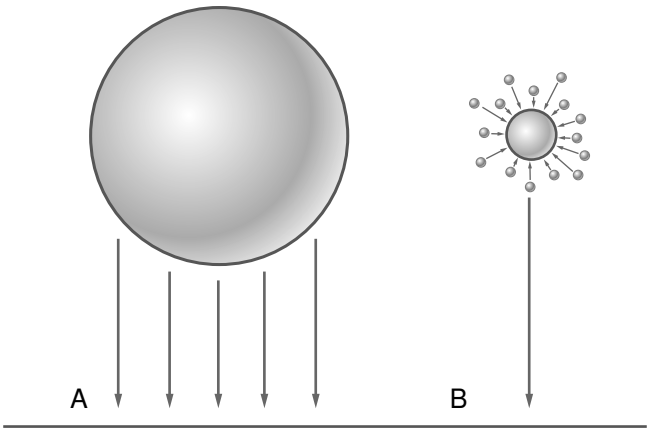
Aerosol particles released in the atmosphere will increase in size as they make their way into the airway as a result of increase in temperature and humidity.

Effect of Temperature and Humidity

Prediction of particle deposition with therapeutic aerosols is complicated further by the fact that the aerosol is generated under relatively dry ambient conditions and then taken into the airway, where temperature and humidity rapidly increase to saturation at 37°C. Inhaled aerosol drugs are not only heterodisperse in size but are also *hygroscopic* (i.e., readily absorbing moisture). Between ambient and BTPS (body temperature, ambient pressure, saturated) conditions, the MMAD of cromolyn sodium powder particles



• **Fig. 3.4** Range of particle size for common aerosols in the environment and the influence of inertial impactions, sedimentation, and diffusion. (From Kacmarek, R. M., Stoller, J. K., & Heuer, A. J. (2017). *Egan's Fundamentals of Respiratory Care* (11th ed.). St. Louis, Missouri O: Mosby.)



• **Fig. 3.5** Effect of mass on particle size. Large particles **(A)** are more susceptible to the force of gravity than smaller particles **(B)**, which are more affected by the bombardment of molecules deposited by diffusion. (From Kacmarek, R. M., Stoller, J. K., & Heuer, A. J. (2017). *Egan's Fundamentals of Respiratory Care* (11th ed.). St. Louis, Missouri: Mosby.)

from an MDI increases from 2.31 to 3.02 μm.[19,20] Fuller et al.[21] measured 50% less aerosol for ventilator delivery through an endotracheal tube (ETT) when using an in vitro model based on a jet nebulizer in warm, humidified air compared with warm, nonhumidified air.

Aerosol Generators for Drug Delivery

KEY POINT

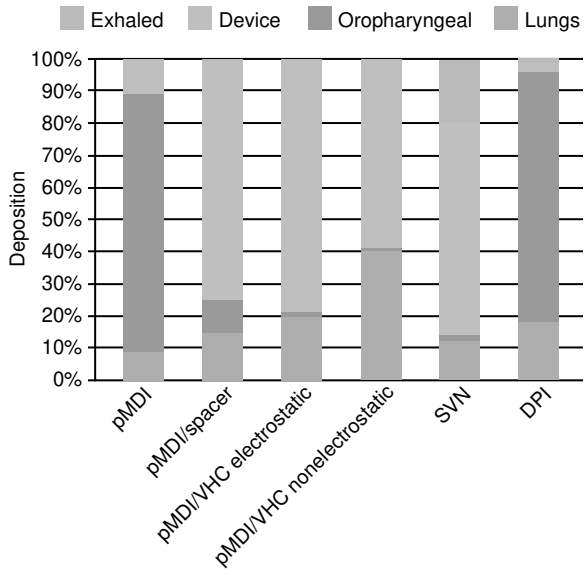
Common devices for the delivery of inhaled aerosol drugs include small volume nebulizers (SVNs), pressurized metered dose inhalers (pMDIs), and dry powder inhalers (DPIs). *Reservoir devices,* such as spacers and holding chambers, can reduce oropharyngeal deposition of a drug and simplify hand–breathing coordination with pMDIs. Proper use of these aerosol-generating devices is necessary to ensure adequate lung delivery, and correct use should be understood by practitioners. Traditional aerosol-generating devices all deliver about 10% to 15% of the dose produced to the lung, although different types of devices vary in their loss patterns.

Lung deposition depends on various factors, such as the aerosol generator, the patient, the drug, and the disease. Depending on the type of SVN used, most of the drug loss with an SVN occurs in the device, whereas the main drug loss with a pressurized metered dose inhaler (pMDI) and DPI is in the oropharyngeal airways. Adding a reservoir device to a pMDI or using a nonelectrostatic valved holding chamber shifts loss from the throat to the reservoir and increases aerosol deposition in the lungs. Lung deposition may range from 1% to 40% with aerosol generators.[22-27] Fig. 3.6 provides the percentages of drug deposition for different aerosol generators, showing that oropharyngeal loss, device loss, and exhalation and ambient loss differ among aerosol device types, as do lung doses.

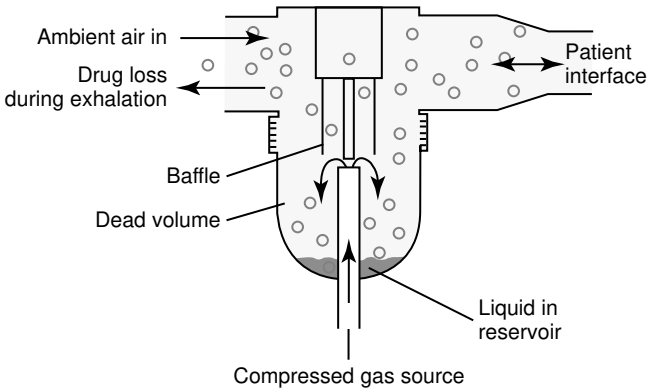
The overall efficiency in lung deposition of 10% to 15% of the total drug dose is not significantly better than with most pMDIs or DPIs used clinically in the past, as discussed subsequently in the section on clinical application and equivalence of various devices. Nebulizers as well as MDIs and DPIs are undergoing an evolutionary transition toward greater efficiency.

Nebulizers

The term **nebulizer** encompasses various devices that operate on different physical principles to generate an aerosol from a drug solution. The SVN is a type of aerosol generator that converts liquid drug solutions or suspensions into aerosol. SVNs are powered by compressed gas (air or oxygen), a compressor, or an electrically powered device.[27] Because jet nebulizers are often used with infants or with patients in acute respiratory distress, slow breathing and an inspiratory pause may not be feasible or obtainable. One of



• **Fig. 3.6** Drug deposition with common aerosol inhaler devices. Shown by color are the varying percentages of drug lung deposition and drug loss in the oropharynx, device, and exhaled breath. *DPI,* Dry powder inhaler; *pMDI,* pressurized metered dose inhaler; *SVN,* small volume nebulizer; *VHC,* valved holding chamber. (From Gardenhire, D. S., Burnett, D., Strickland, S., & Myers, T. R. (2018). *A Guide to Aerosol Delivery Devices for Respiratory Therapists* (4th ed.). Irving, Texas: American Association for Respiratory Care.)



• **Fig. 3.7** Schematic of a small volume jet nebulizer. (Modified from Cairo, J. M. (2014). *Mosby's Respiratory Care Equipment* (9th ed.). St. Louis, Missouri: Elsevier.)

the main advantages of SVNs is that dose delivery occurs over 60 to 90 breaths, rather than in one or two inhalations. A single ineffective breath does not destroy the efficacy of the treatment. Box 3.2 summarizes the advantages and disadvantages of SVNs.

Types of Small Volume Nebulizers

SVNs can be classified into three categories[27]:

1. Jet (pneumatic) nebulizers
2. Mesh nebulizers
3. Ultrasonic nebulizers (USNs)

Jet (Pneumatic) Nebulizers. Jet (pneumatic) nebulizers are small-reservoir, gas-powered (pneumatic) aerosol generators, also referred to as *handheld nebulizers, updraft nebulizers, or unit-dose nebulizers.* The traditional jet nebulizer is commonly used and exhibits a large amount of drug wastage, especially within the device itself; see Fig. 3.7 for a generic illustration. Jet nebulizers use a jet-shearing principle for creation of an aerosol from the drug solution. An external source of compressed gas is directed through a narrow orifice inside the reservoir cup. The expanding gas creates a localized negative pressure, drawing the drug solution up feeder tubes. As the liquid enters the gas stream, droplets are formed from gas turbulence and impaction on baffles. Smaller particle sizes are emitted after the baffling process. Larger liquid particles are recirculated back to the reservoir. There is significant evaporation of the aqueous solution with gas-powered nebulization. Nebulizer temperatures can fall from ambient to approximately 10°C within minutes because of the latent heat of vaporization. With evaporation and constant recirculation, drug solute becomes increasingly concentrated, up to 150% to 300% of the original concentration.[28]

Pneumatic jet nebulizers have been conceptualized into four categories[27-29]:

1. Jet nebulizer with reservoir tube
2. Jet nebulizer with collection bag/elastomeric ball
3. Breath-enhanced jet nebulizer
4. Breath-actuated jet nebulizer

Fig. 3.8 illustrates the types of pneumatic jet nebulizers and their aerosol outputs.

Jet Nebulizer With Reservoir Tube. A jet nebulizer with reservoir tube is the traditional, least expensive, and most widely used nebulizer in which aerosol is produced constantly during inspiration, expiration, and breath hold.[28,30] Although the addition of 6 inches of reservoir tubing reduces the release of aerosol to ambient air during exhalation and breath hold, it does not eliminate ambient contamination. These nebulizers provide a low percentage of the dose to the patient and have been considered to be inefficient because only 10% to 20% of the emitted dose is inhaled. The Misty-neb (Cardinal Health, Dublin, Ohio) and the Neb U mist

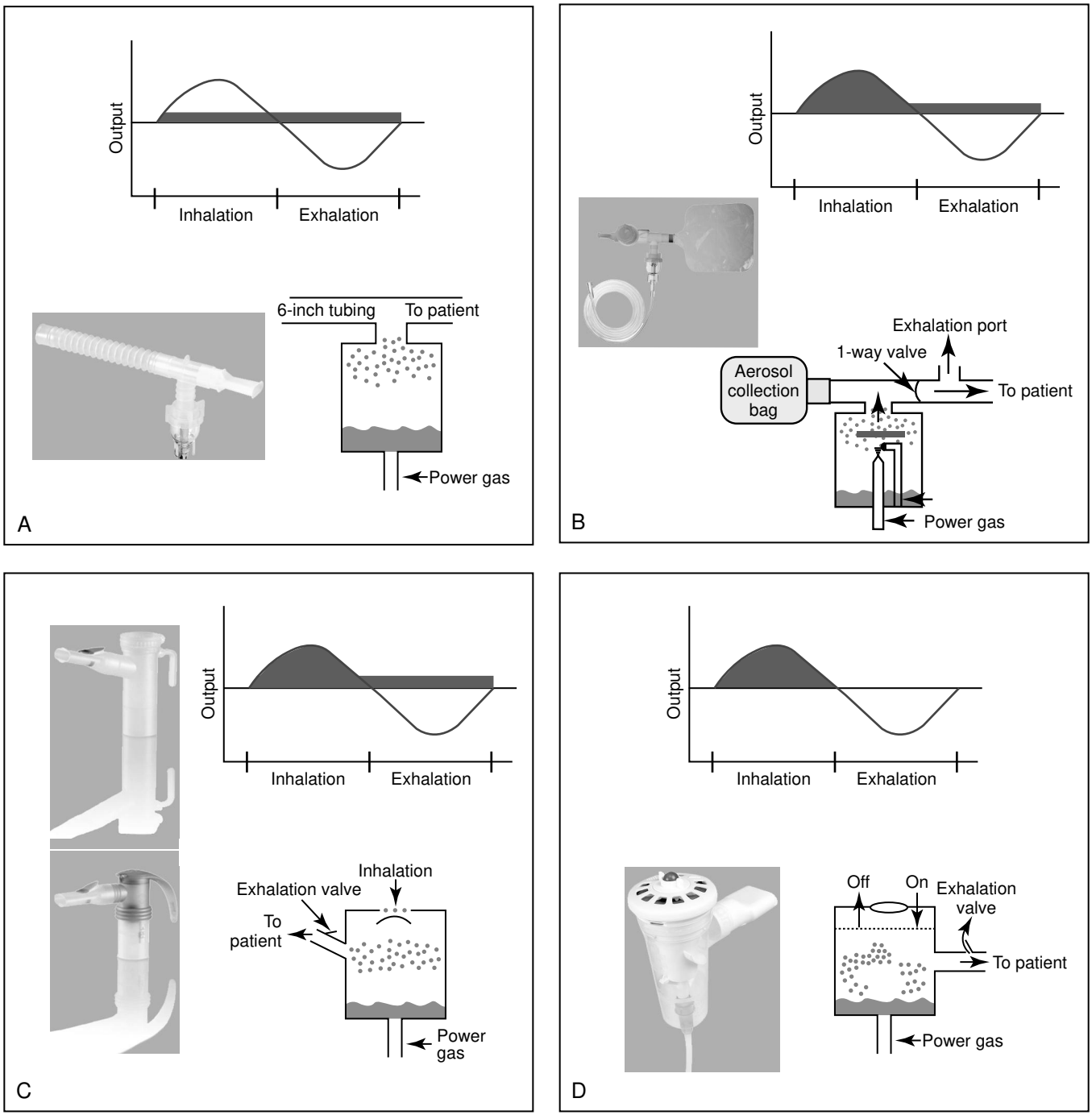
• BOX 3.2 Advantages and Disadvantages of Small Volume Nebulizers

Advantages

- Ability to aerosolize many drug solutions.
- Ability to aerosolize drug mixtures (i.e., more than one drug) with suitable testing of drug activity.
- Minimal cooperation or coordination required for inhalation.
- Useful in very young or very old patients, debilitated patients, and patients in acute distress.
- Effective with low inspiratory flows or volumes.
- Normal breathing pattern can be used, and inspiratory pause (breath hold) not required for efficacy.
- Drug concentrations and dose can be modified, if desired.

Disadvantages

- Equipment required for use is expensive and cumbersome.
- Treatment times are somewhat lengthy, ranging from 5 to 25 minutes, depending on the type of small volume nebulizer used for aerosol drug delivery.
- There is variability in performance characteristics among different types, brands, and models.
- Contamination is possible with inadequate cleaning.
- Assembly and cleaning are required.
- Wet, cold spray occurs with mask delivery.
- Aerosol drug administration with a face mask may inadvertently deposit in the eyes, resulting in eye irritation.
- Power source (compressed gas, battery, or electricity) is needed for aerosol drug administration.



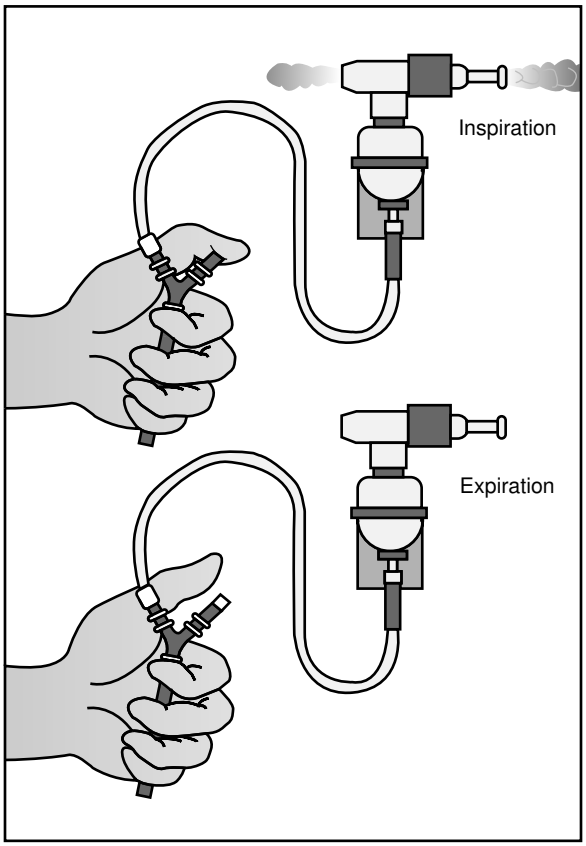
• **Fig. 3.8** Different types of pneumatic jet nebulizer designs and their aerosol output, indicated by *shaded area.* **A,** Pneumatic jet nebulizer with reservoir tube. **B,** Jet nebulizer with collection bag. **C,** Breath-enhanced jet nebulizer. **D,** Breath-actuated jet nebulizer. (Modified from Gardenhire, D. S., Burnett, D., Strickland, S., & Myers, T. R. (2018). *A Guide to Aerosol Delivery Devices for Respiratory Therapists* (4th ed.). Irving, Texas: American Association for Respiratory Care.); **A** *inset,* From DeVilbiss Healthcare, Somerset, Pennsylvania; **B** *inset,* From Westmed, Inc., Tucson, Arizona; **C** *inset,* From PARI Respiratory Equipment, Inc., Midlothian, Virginia; **D** *inset,* AeroEclipse II Breath Actuated Nebulizer [BAN], From Trudell Medical International, London, Ontario, Canada.)

(Hudson RCI, Durham, North Carolina) are examples of this type of jet nebulizer.

Jet Nebulizer With Collection Bag or Elastomeric Ball. A jet nebulizer with collection bag produces aerosol by continuously filling a collection bag, and no aerosol is lost during expiration because of the one-way inspiratory valve between the nebulizer and the mouthpiece. Through an inspiratory valve, the patient inhales aerosol from the collection bag and exhales to the atmosphere through the exhalation port placed between the one-way inspiratory valve and the mouthpiece.[27,30] The Circulaire II (Westmed, Inc., Tucson,

Arizona) is one model of a jet nebulizer with collection bag. The Circulaire Hybrid (Westmed, Inc., Tucson, Arizona) contains a soft elastomeric ball as the reservoir. The ball is simple to remove and easily washed and dried, which facilitates home use.

Breath-Enhanced Jet Nebulizer. Breath-enhanced jet nebulizers allow more aerosol release during inspiration with decreased output during exhalation or breath hold through two one-way valves used to prevent the loss of aerosol to the environment. Although aerosol is produced during inspiration and expiration, the inspiratory valve opens and gas vents through the nebulizer only when the patient inhales. Expired gas is routed through a one-way valve in the mouthpiece; aerosol is contained in the reservoir and there is reduced ambient loss. Pari LC Plus (PARI Respiratory Equipment, Inc., Midlothian, Virginia), NebuTech (Salter Labs, Arvin, California), and Ventstream Pro (Phillips Healthcare, Andover, Massachusetts) are examples of breath-enhanced nebulizers.



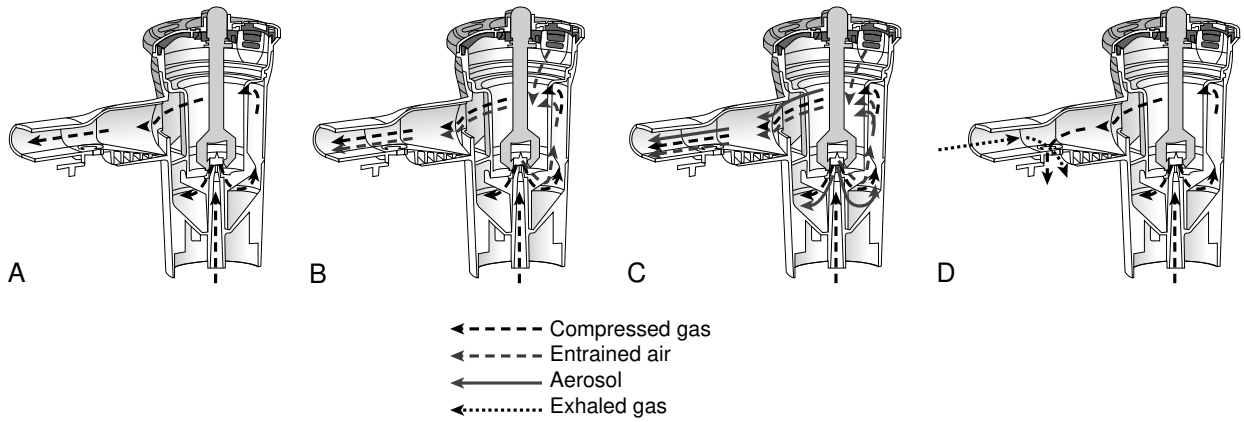
• **Fig. 3.9** Schematic illustration of the function of a manual breath-actuated jet nebulizer. Use of a finger control regulates production during inspiration and expiration. (From Cairo, J. M. (2014). *Mosby's Respiratory Care Equipment* (9th ed.). St. Louis, Missouri: Elsevier.)

Breath-Actuated Jet Nebulizer. Breath-actuated jet nebulizers release aerosol only during inspiration because they are designed to increase aerosol drug delivery to patients by reducing loss of medication during expiration. Although breath-actuated nebulizers increase the inhaled dose by more than threefold, their efficiency is achieved by an increase in dosing time.[30] The two types of breath-actuated nebulizers are[27]:

1. Manual breath-actuated jet nebulizers
2. Mechanical breath-actuated jet nebulizers

Manual Breath-Actuated Jet Nebulizer. Manual breath-actuated jet nebulizers represent the first generation of breath-actuated nebulizers, which regulate aerosol production during inspiration and expiration through use of a patient-controlled thumb port. In manual breath-actuated nebulizers, dose delivery occurs only during inspiration; the thumb control is blocked so that there is no nebulization during expiration. Releasing the thumb at the port pauses the nebulization. Even though this type of nebulizers reduce drug loss during expiration, they require good hand–breath coordination and significantly increase the treatment time.[25-27] Fig. 3.9 illustrates the relationship of nebulizer generation with a manual breath-actuated jet nebulizer.

Mechanical Breath-Actuated Jet Nebulizer. Mechanical breath-actuated jet nebulizers have a breath-actuated valve that is triggered by patients creating an inspiratory force (Fig. 3.10). When the breath-actuated valve is triggered, aerosol is produced only during inspiration. This type of nebulizer eliminates the need for a collection bag or reservoir.[27,30] The AeroEclipse II (Trudell Medical International, London, Ontario, Canada) is an example of a mechanical breath-actuated nebulizer. The AeroEclipse II is also available in a reusable nebulizer (R BAN; Trudell Medical International, London, Ontario, Canada).



• **Fig. 3.10** Schematic illustration of the function of a mechanical breath-actuated nebulizer. **A,** Before inhalation. **B,** Patient inhales, and actuator starts to move down. **C,** Negative pressure pulls the diaphragm down (with actuator moved down, sealing around the nozzle cover), producing aerosol. **D,** Patient exhales through valve in mouthpiece. As pressure increases, the diaphragm and actuator move up, stopping aerosol production. (From Trudell Medical International, London, Ontario, Canada.)

Mesh Nebulizers. Mesh nebulizers move the liquid formulations through a fine plate or mesh with multiple apertures (small holes) to generate aerosol. These nebulizers have no internal baffling mechanism and create aerosol by using the aperture plate or the ultrasonic horn. The diameter of the apertures determines the size of the particle generated. Mesh nebulizers do not require a gas source because they are powered by battery or electricity, and they leave very little dead volume (0.1–0.5 mL) in the nebulizer, so they are very efficient. There are two types of mesh nebulizers on the market[25-27]:

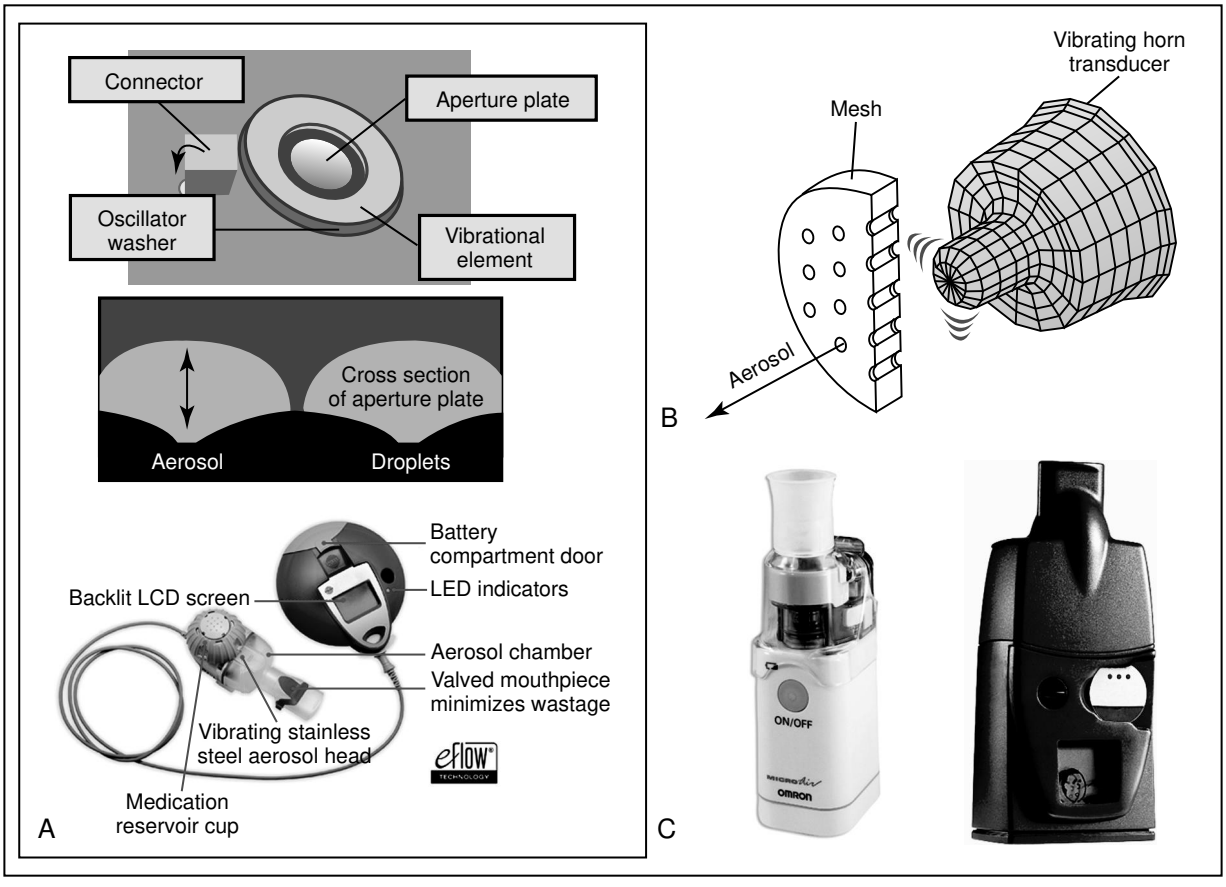
1. Active vibrating mesh nebulizers
2. Passive mesh nebulizers

Active Vibrating Mesh Nebulizer. Active vibrating mesh nebulizers (VMNs) have an aperture plate with greater than 1000 funnel-shaped holes on an electroformed sheet that is vibrated by a piezo-ceramic element that surrounds the aperture plate.[25-27,31] The Aeroneb Solo and Pro (Aerogen, Galway, Ireland) and eFlow (PARI Respiratory Equipment, Inc., Midlothian, Virginia) are examples of active VMNs (Fig. 3.11).

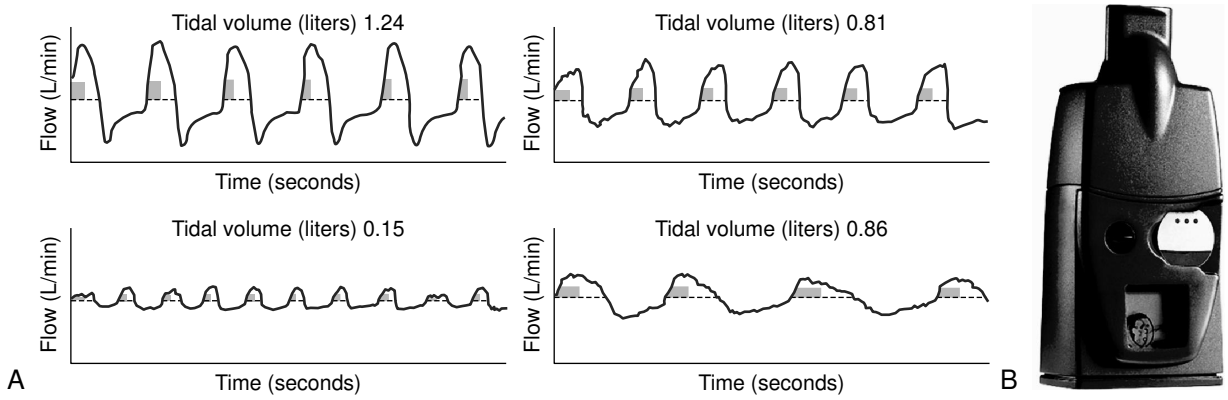
Passive Mesh Nebulizer. Passive mesh nebulizers use an ultrasonic horn to push fluid through the mesh. An example of passive mesh nebulizer is the adaptive aerosol delivery (AAD) system, such as the I-neb (Phillips Healthcare, Andover, Massachusetts). I-neb is a small, battery-operated, lightweight, and silent aerosol generator designed to deliver a precise and reproducible dose of drug. After aerosol is injected into the breath at the beginning of inhalation, the dosage of the drug is controlled through an AAD disk and specific metering chamber that delivers a preset volume ranging from 0.25 to 1.4 mL with a residual volume of about 0.1 mL[25-27] (Fig. 3.12). In addition, the I-neb incorporates an AAD algorithm that pulses medication delivery into 50% to 80% of each inspiration based on a rolling average of the last three breaths. On successful delivery of the medication, the I-neb provides continuous audible and tactile feedback to the patient through a liquid crystal display.[27]

Ultrasonic Nebulizers. USNs are electrically powered devices operating on the piezoelectric principle and capable of high output. Particle sizes vary by brand. Fig. 3.13 is a generic illustration of a USN. Although these devices have not been used as routinely as other types (described below) for aerosolization of drugs, they have been reintroduced as small, portable units that can operate on direct current (DC) voltage. Such units have several advantages and some disadvantages, as listed in Box 3.3.

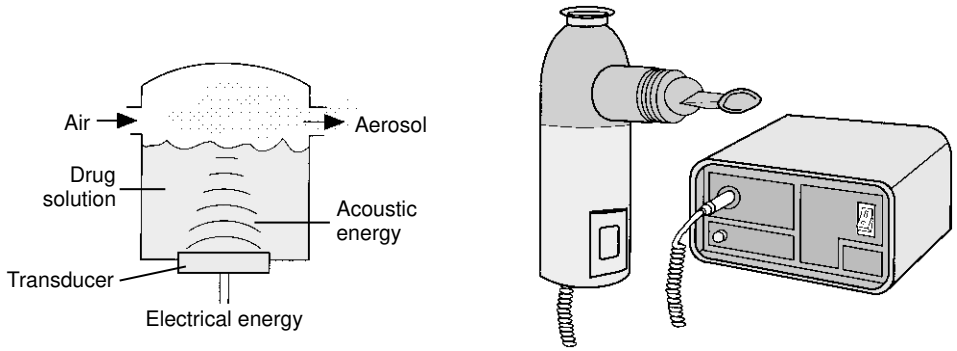
At the frequencies used in medical devices, there are several effects with the potential for altering drug activity of the nebulizer solution. Most of the energy produced during ultrasonic nebulization is dissipated as heat. Protein and other heat-sensitive (or *thermolabile*) formulations can be denatured by heat, especially if the melting temperature of the protein is reached. For example, insulin was shown to be inactivated by USN use.[32] Most currently available inhaled drugs are stable with use of a USN.[33] However, the breakdown of a drug can be a cumulative effect of surface denaturation, heat, cavitation, and direct pressure effects in a USN.[33] Drug solutions must be tested by using ultrasonic delivery to determine that activity is preserved, particularly when proteins or



• **Fig. 3.11** Basic configurations of mesh nebulizer. **A,** Active vibrating mesh. **B,** Ultrasonic horn. **C,** Passive mesh. (**A,** Courtesy of PARI Respiratory Equipment, Inc., Midlothian, Virginia. **B and C,** Courtesy Omron Healthcare Inc., Bannockburn, Illinois.)



• **Fig. 3.12 A,** Aerosol is injected into the breath at the beginning of inspiration. Adaptive aerosol drug delivery through a passive mesh nebulizer, such as I-neb **(B)**. (From Cairo, J. M. (2014). *Mosby's Respiratory Care Equipment* (9th ed.). St. Louis, Missouri: Elsevier; *photo inset,* courtesy Phillips Healthcare, Andover, Massachusetts.)



• **Fig. 3.13** Illustration of the principle of ultrasonic nebulization, with an example of a portable device used to aerosolize medications.

• BOX 3.3 Advantages and Disadvantages of Portable Ultrasonic Drug Nebulizers

Advantages

- Small size
- Rapid nebulization with shorter treatment times
- Smaller drug amounts with no diluent for filling volume
- Can be used during car travel or camping

Disadvantages

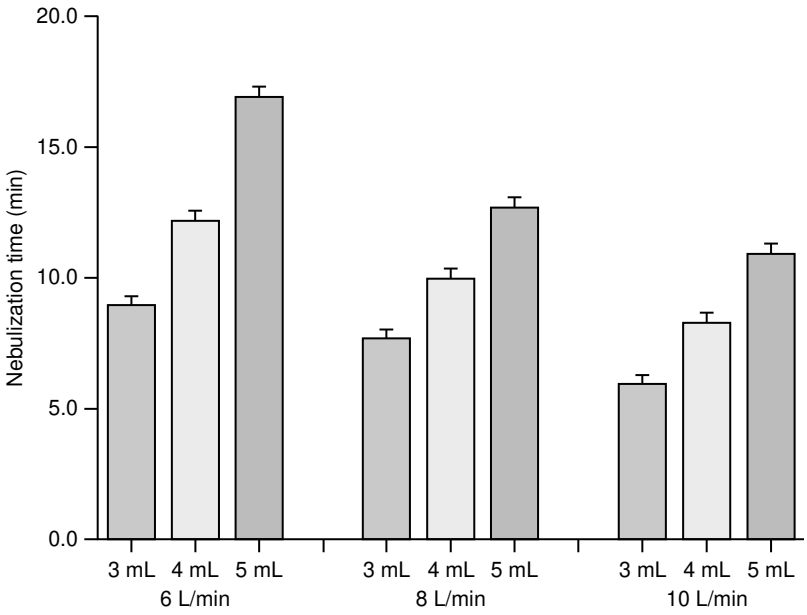
- High expense
- Fragility, lack of durability
- Requires electrical source (either AC or DC)
- Possible degrading effect on drug must be determined

AC, *Alternating current;* DC, *direct current.*

liposomes are nebulized. The clinician should refer to the manufacturer's directions to help determine which device should be used for each drug.

Factors Affecting Jet Nebulizer Performance. When using a jet nebulizer, it is important to control factors affecting jet nebulizer performance during aerosol drug administration. Various types of jet nebulizers are available on the market, and several studies have indicated that performance varies among products from different manufacturers and even among nebulizers from the same manufacturers.[34-36] These factors include residual volume or "dead volume," filling volume, treatment time, flow rate and pressure, output rate, continuous versus inspiratory nebulization, type of power gas, physical nature of the solution to be nebulized, humidity, temperature, and device interface. Some of these factors are reviewed in greater detail below.

Dead Volume (Residual Volume). Jet nebulizers do not aerosolize below a minimal volume, termed the dead volume, which is the amount of drug solution remaining in the reservoir when the device begins to sputter and aerosolization ceases. This volume can vary with the brand of nebulizer but is in the order of 0.5 to 1.0 mL. This is the primary reason why diluent, which is effectively additional volume, is added to 0.5 mL of a bronchodilator solution, such as albuterol. Adding diluent does not alter the amount of drug (dose) in the nebulizer; it simply "expands" the solution volume. The concentration of the solution is less, not the amount of drug (see Chapter 4 for further discussion). Drug loss with nebulization can also occur into the ambient air. As a result of these factors, the amount of dose available to be inhaled from a nebulizer is considerably less than the dose placed into the reservoir. Kradjan and Lakshminarayan[37] found that under clinical conditions of nebulization until sputter, approximately 35% to 60% of a drug solution was delivered from the nebulizer. Even with vigorous agitation, this amount increased to only 53% to 72%. A study by Shim and Williams[38] found that only 40% to 52% of the total



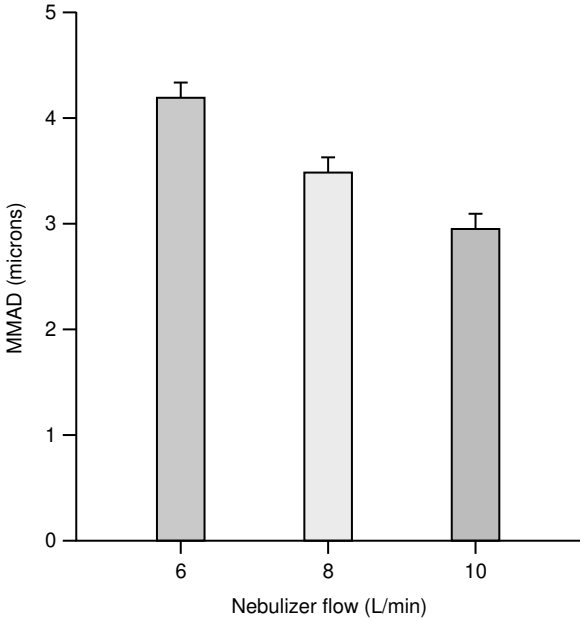
• **Fig. 3.14** Relationship of volume and flow rate to time of nebulization averaged for 17 gas-powered nebulizers. (From Hess, D., Fisher, D., Williams, P., et al. (1996). Medication nebulizer performance: effects of diluent volume, nebulizer flow, and nebulizer band. *Chest,* 110, 498.)

dose was delivered from gas-powered nebulizers. In a positive-pressure circuit, this efficiency may decrease further, to approximately 30% of the total dose.[39] Evaporation of an aqueous solution not only causes cooling of the nebulizer and liquid but also can increase the concentration of solute in the residual (dead) volume.

Filling Volume and Treatment Time. Based on the work of Hess and associates,[35] Fig. 3.14 shows the relationship of volume and flow rate to the time of nebulization, presented as the pooled average performance of 17 nebulizer brands. Increasing the volume increases the time of effective nebulization at any given flow rate. At less than 2 mL, most pneumatic nebulizers do not perform well because the volume is close to the dead volume—that is, the residual amount that does not nebulize. At 6 mL, an excessively long time is required for treatment (>10 minutes) with most brands. Although 5 minutes seems to be a short time, even this can be inconveniently long as a way of taking medication three or four times a day; some patients have difficulty in taking a pill four times a day, an approximately 2- to 3-second activity. Patient compliance is directly proportional to convenience. Given the volume requirements of nebulizers for efficient operation and the need for relatively brief treatments, a volume between 3 and 5 mL of solution is recommended, unless the nebulizer is specifically designed for a smaller fill volume. Increasing the volume also decreases the concentration of a drug remaining in the dead volume when nebulization ceases.[35] The dose of a drug available to the patient is increased, although treatment times also increase at any given flow rate.

Increasing fill volume increases inhaled efficiency and the dose to the patient. It should be noted that the approved label dose of the drug includes the fill volume that was used in the clinical trials that lead to approval by the U.S. Food and Drug Administration (FDA). Increasing fill volume would increase the dose to the patient and should not be done without consulting with the prescribing physician.

Effect of Flow Rate and Pressure. A second practical question concerns the flow rate at which to power jet nebulizers. The flow



• **Fig. 3.15** Effect of power gas flow rate on the mass median aerodynamic diameter (MMAD) of aerosol particles produced on average by 17 gas-powered nebulizers. (From Hess, D., Fisher, D., Williams, P., et al. (1996). Medication nebulizer performance: effects of diluent volume, nebulizer flow, and nebulizer band. *Chest,* 110, 498.)

rate affects two variables: the length of treatment time and the size of the particles produced. Fig. 3.14 illustrates the interaction between volume and the flow rate in determining the time of nebulization. At a flow rate of 6 L/min, a volume of 3 mL requires less than 10 minutes; at 10 L/min, a volume of 5 mL can be nebulized in approximately 10 minutes. Fig. 3.15 shows the effect of flow rates on particle size of the aerosol produced, averaged for the 17 nebulizers studied by Hess et al.[35] With pneumatically

powered nebulizers, increasing the flow rate decreases the particle size and shifts the MMAD lower. On the basis of the results of Hess et al. shown in Figs. 3.14 and 3.15, average optimal rates are a filling volume of 5 mL and a flow rate of 6 to 8 L/min for many nebulizers. Also, each model of jet nebulizer is designed to work best at a specific flow, ranging from 2 to 8 L/min. It is important to operate a jet nebulizer with a compressor or a gas flow that matches the intended design; at a lower flow or pressure, particle size would increase. If a jet nebulizer designed to operate at 6 to 8 L/min at 50 pounds per square inch (psi) is driven by a compressor producing 13 psi, it will produce a larger particle size, which will influence efficiency.[27]

Type of Power Gas. Use of gases other than oxygen or air can change the performance characteristics of a nebulizer. Hess et al.[35] showed that the use of heliox (a mixture of helium and oxygen) to nebulize albuterol caused particle size and inhaled drug mass to decrease, along with a greater than twofold increase in nebulization time. Increasing the flow of heliox returned output to that seen with air.[40] The flow rate should be increased by 1.5 to two times during heliox-driven aerosol drug administration to bring particle size and output back to levels achieved with air or oxygen.[27,41,42] Selection of the appropriate gas to power a nebulizer needs to be done by the practitioner on the basis of patient data or policy and procedure set by the institution. Oxygen has always been used because of its availability; however, using air to control the oxygen a patient receives may be of importance to practitioners.

Device Interface. Device interfaces used for aerosol drug administration include mouthpieces and face masks. Ideally, a mouthpiece should be used because studies suggest that the mouthpiece provides greater lung dose than a standard pediatric aerosol mask.[43,44] Also, use of a face mask increases the amount of aerosol deposited on the face, in the eyes, and into the nose, which can be particularly significant for certain drugs, such as inhaled corticosteroids. A mouthpiece cannot be used by infants and children, and it is also uncomfortable for longer aerosol therapy. Regardless of the type of device interface used during aerosol therapy, patients should be instructed to inhale through the mouth because the nose tends to filter more aerosol compared with the mouth.[27]

Type of Solution. Droplet size of nebulized solutions is related to surface tension and viscosity of the solution and is partially determined as well by the baffles in the device.[45] Recommended filling volumes and flow rates are suitable for the aqueous bronchodilator solutions usually administered with these devices. However, the volumes and flow rates suggested may require modification for some drug solutions, such as pentamidine or antibiotics, which have different physical characteristics and viscosities. For example, higher viscosity antibiotic solutions of gentamicin or carbenicillin require power gas flow rates of 10 to 12 L/min to produce suitably small aerosol particles for inhalation with some jet nebulizers.[46] Some disposable nebulizers may exhibit greater variability in performance or not achieve adequate output characteristics with new or nonbronchodilator drug solutions. The performance of a jet nebulizer should be tested with various drug solutions, and newly introduced nebulizer drugs should be tested with an intended nebulizer system to ensure adequate performance. It is best to nebulize only drugs that have been manufactured for nebulization; however, it is common to nebulize agents intended for a different route of administration. Nebulizers not tested for performance with a new or unknown drug solution cannot be assumed to produce adequate output and particle sizes. As indicated in Chapter 2 in the review of lung availability/total systemic availability (L/T) ratios and the pharmacokinetics of inhaled aerosol drugs, efficiency of lung delivery is a function of *both* drug and device. The drug–device combination should be tested before clinical use.

Table 3.1 lists some tested and adequate drug–device combinations for nebulizer delivery. Additives to the drug solution can also affect aerosol characteristics and drug delivery.[27] See Box 3.4[47] for helpful information on the use and cleaning of jet nebulizers.

Pressurized Metered Dose Inhalers

The pMDIs has been in use since its development by Maison in 1955.[48] These devices are most commonly aerosol generators prescribed for patients with asthma and chronic obstructive pulmonary disease (COPD); they are small, pressurized canisters for oral or nasal inhalation of aerosol drugs and contain multiple doses of accurately metered drug. Advantages and disadvantages of drug delivery by pMDI are listed in Box 3.5.

Technical Description

A pMDI has five major components:

1. Canister
2. Propellant/excipient mixture
3. Drug formulary
4. Metering valve
5. Actuator and dose counter

Fig. 3.16 illustrates the major components of a pMDI as well as the function of the metering valve. The characteristics of each pMDI component are described in Table 3.2.

The drug in a pMDI is either a suspension of micronized powder in a liquefied propellant or a solution of the active ingredient in a cosolvent (usually ethanol) mixed with the propellant. Dispersing agents, or *surfactants,* are added to prevent aggregation of drug particles and to lubricate the valve mechanism, thereby maintaining

TABLE 3.1 Representative Drug–Device Combinations Tested for Nebulizer Drug Delivery

Drug	Approved Nebulizer
Bronchodilator	Nebulizer type not specified
Acetylcysteine	Nebulizer type not specified
Budesonide (Pulmicort Respules)	Should not be used with ultrasonic nebulizer
Tobramycin (Bethkis, TOBI)	Pari LC
Aztreonam (Cayston)	Altera Nebulizer System
Dornase alfa (Pulmozyme)	Hudson T Up-draft II, Marquest Acorn II, Pari LC, Durable Sidestream, Pari Baby
Pentamidine (NebuPent)	Marquest Respirgard II
Ribavirin (Virazole)	Small particle aerosol generator (SPAG)
Iloprost (Ventavis)	ProDose or I-neb
Treprostinil (Tyvaso)	Tyvaso Nebulizer System
glycopyrrolate (LONHALA)	MAGNAIR

From Gardenhire, D. S., Burnett, D., Strickland, S., Myers, T. R. (2018). *A Guide to Aerosol Delivery Devices for Respiratory Therapists* (4th ed.).Irving, Texas: American Association for Respiratory Care.

• BOX 3.4 Use of Small Volume Nebulizers

Generic Recommendations That Apply to All Nebulizers[27]

1. Read and follow instructions before using nebulizer.
2. Ensure that nebulizer is properly assembled, according to the manufacturer's instructions.
3. Ensure that nebulizer is cleaned and dried between treatments.
4. Ensure that nebulizer is operated in its proper orientation.

Critical Steps in Jet Nebulizer Use27

1. Assemble all parts of nebulizer before treatment including tubing, nebulizer cup, and mouthpiece or mask.
2. Put drug into nebulizer cup.
3. Sit in the upright position.
4. Connect nebulizer to power source, such as compressed air, oxygen, or a compressor.
5. Breathe normally during treatment, taking occasional deep breaths until sputter occurs or until end of nebulization.
6. Keep nebulizer in vertical position during treatment.
7. Rinse nebulizer with sterile or distilled water.
8. Allow to air dry.

Critical Steps in Vibrating Mesh and Ultrasonic Nebulizer Use[27]

1. Correctly assemble nebulizer according to the manufacturer's instructions.
2. Follow the manufacturer's instructions in performing functionality test before first use of the new nebulizer and after each disinfection to verify proper operation.
3. Place medicine into medication reservoir. Do not exceed volume recommended by manufacturer.
4. Sit in upright position.
5. Turn on power.
6. Hold nebulizer in position recommended by the manufacturer.
7. Breathe normally during treatment, taking occasional deep breaths.
8. Turn off unit to avoid waste if treatment must be interrupted.
9. Disassemble and clean he nebulizer after treatment, as recommended by the manufacturer.
10. When using VMN, do not touch vibrating mesh during cleaning because it will damage unit.
11. Disinfect nebulizer, according to the manufacturer's instructions, once or twice a week.

Common Errors in Use27

- Failure to assemble nebulizer properly
- Wasting dose by tilting (some nebulizers)
- Failure to keep mouthpiece in mouth during treatment
- Failure to mouth breathe during nebulization

Cleaning Instructions for Small Volume Nebulizers[27]

VMNs and USNs should be cleaned and disinfected according to the manufacturer's instructions. During the cleaning of VMNs, the mesh should not be touched to prevent damage to the unit. For jet nebulizers, the Cystic Fibrosis Foundation guidelines[47] recommend washing the parts of jet nebulizers with soap and hot water after each treatment, taking care to avoid damaging any parts of the aerosol generator. Also, nebulizers should be cleaned after every treatment at home. The longer a dirty nebulizer sits and is allowed to dry, the harder it will be to clean thoroughly. Rinsing and washing the nebulizer immediately after each treatment reduces the risk of infection. Cleaning instructions for the jet nebulizer are as follows:

Cleaning Instructions for the Jet Nebulizer[27]

Cleaning After Each Use

- Wash hands before handling equipment.
- Disassemble parts after every treatment.
- Remove tubing from compressor and set aside; tubing should not be washed or rinsed.
- Rinse nebulizer cup and mouthpiece with either sterile water or distilled water.
- Shake off excess water.
- Air dry on absorbent towel.
- Store nebulizer cup in resealable plastic bag.

Cleaning Once or Twice a Week

- Wash hands before handling equipment.
- Disassemble parts after every treatment.
- Remove tubing from compressor and set aside; tubing should not be washed or rinsed.
- Wash nebulizer parts in warm water with liquid dish soap.
- Disinfect nebulizer, according to manufacturer's instructions; nebulizer parts may be soaked in one of the following solutions:
  1. 1 part household bleach in 50 parts water for 3 minutes
  2. 70% isopropyl alcohol for 5 minutes
  3. 3% hydrogen peroxide for 30 minutes
  4. 1 part distilled white vinegar in 3 parts hot water for 1 hour (not recommended for patients with cystic fibrosis)
- Rinse parts with sterile or distilled water.
- Shake off excess water and place all parts on clean paper towel.
- Allow parts to air dry completely on absorbent towel.
- Reassemble nebulizer and store in clean dry bag or container.

USN, *Ultrasonic nebulizer;* VMN, *vibrating mesh nebulizer.*

From Gardenhire, D. S., Burnett, D., Strickland, S., Myers, T. R. (2018). A Guide to Aerosol Delivery Devices for Respiratory Therapists *(4th ed.). Irving, Texas: American Association for Respiratory Care.*

suitable particle sizes in the aerosol plume, aerosol particles discharged from a pMDI, produced in CFC (e.g., Freon) devices. These surfactants are not soluble in HFA devices.[49] In his report, Newman[50] presented a detailed technical description of the complexities involved in producing a pMDI.

Chlorofluorocarbon versus Hydrofluoroalkane Propellants

Historically CFCs and HFAs were the two types of propellants that are used with pMDIs. In the past, blends of liquefied gas (CFCs) were used with pMDIs to create an aerosol, but because one CFC molecule can destroy 100,000 molecules of stratospheric ozone, the FDA banned the use of CFC-pMDIs. The few remaining CFC aerosol devices were removed from market on December 31, 2013. Hydrofluorocarbons (HFCs), or *HFAs,* were then identified as propellants that were nontoxic to the atmosphere and to the patient and that also had properties suitable for MDI aerosol generation. In particular, HFA 134a has a vapor pressure similar to that of CFC 12. The structure of HFA 134a is illustrated in Fig. 3.17 and compared with that of CFC 12. Replacement of CFC propellants has led to overall reengineering of pMDI components (valve, seals, exit orifice, and drug formulation), which