SEVENTH EDITION

PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

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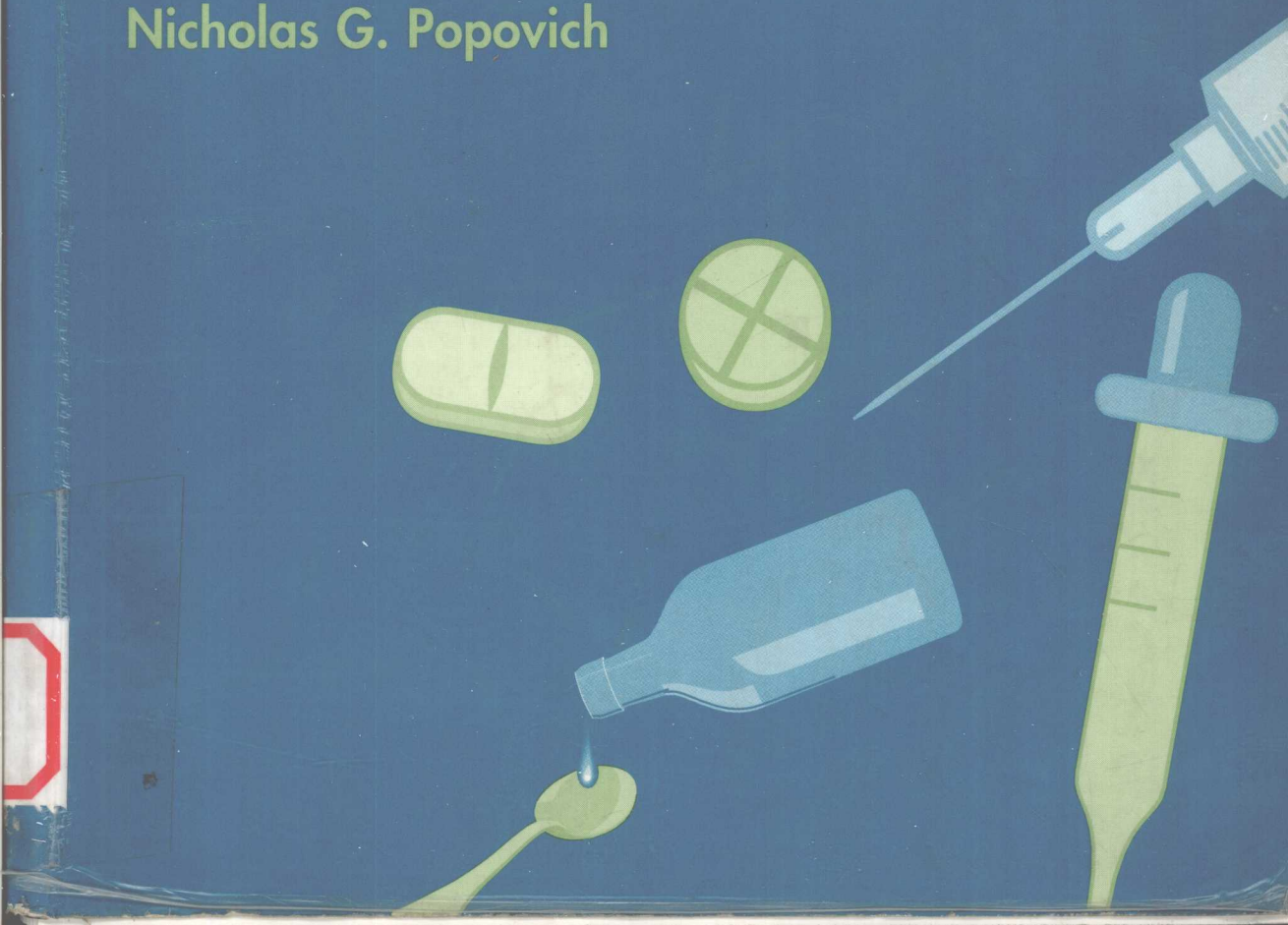

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PHARMACEUTICAL DOSAGE FORMS AND DRUG DELIVERY SYSTEMS

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Preface

The purpose of this text is to introduce pharmacy students to the basic pharmaceutic principles and technologies applied in the preparation of pharmaceutical dosage forms and drug delivery systems. An integrated presentation is used to demonstrate the interrelationships which exist between pharmaceutic and biopharmaceutic principles, product design, formulation, manufacture, and the clinical application of the various dosage forms in patient care.

As has been the hallmark of this textbook since its first edition some thirty years ago, each chapter is written at a level consistent with the requirements of students being introduced to this academic area of study. Because this textbook often is used early in the professional curriculum, important introductory topics are included as the historical development of drugs and pharmacy; the role of the pharmacist in contemporary practice; standards of the *United States Pharmacopeia/National Formulary;* systems and techniques of pharmaceutical measurement; basic pharmaceutic and biopharmaceutic principles applicable to drug product development; current good manufacturing practice and current good compounding practice standards; and the regulatory process by which pharmaceuticals are approved for marketing by the federal Food and Drug Administration.

The Seventh Edition represents a complete rewrite of the previous edition and the reorganization of the various chapters into seven divisions based upon traditional pharmaceutic pedagogy. This allows the systematic presentation of dosage forms according to their physical form and characteristics. The "Physical Pharmacy Capsules," introduced in the Sixth Edition to emphasize important underlying pharmaceutic principles have been expanded in the new edition. Other important changes include enhanced considerations of dosage form design and formulation, a new section on current good compounding practices, expanded clinical considerations in the use of each dosage form, and a new chapter on "Novel Dosage Forms and Drug Delivery Technologies." Also new with this edition is the "chapter-at-a-glance" format at the beginning of each chapter.

Acknowledgments

I acknowledge with grateful appreciation the major contributions of co-authors Loyd V. Allen, Jr. and Nicholas G. Popovich in sustaining the vitality of this work. Their respective expertise in the fields of physical pharmacy and formulation technology and in clinical pharmacy and pharmacy practice has allowed the integrated approach utilized in this work. Together, we extend our gratitude to students and colleagues who have shared their thoughts with us on this revision and trust that we have been successful in responding to their suggestions. We also acknowledge with appreciation, our colleagues in industry who generously have provided scientific and technical information and updated figures for our use. We especially thank our friends at Lippincott Williams & Wilkins who have contributed so expertly to the planning, preparation, and production of this new edition, namely Donna Balado, Acquisitions Editor; Jennifer Schmidt, Managing Editor; Karen Gulliver, Freelance Managing Editor, and Susan Rockwell, Production Manager, Copyediting.

HOWARD C. ANSEL
Athens, Georgia

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1 INTRODUCTION TO DRUGS AND PHARMACY

Chapter at a Glance

A DRUG is defined as an agent intended for use in the diagnosis, mitigation, treatment, cure, or prevention of disease in humans or in other animals. One of the most astounding qualities of drugs is the diversity of their actions and effects on the body.

This quality enables their selective use in the treatment of a range of common and rare conditions involving virtually every body organ, tissue, and cell.

Some drugs selectively stimulate the cardiac muscle, the central nervous system, or the gastrointestinal tract, whereas other drugs have the opposite effect. Mydriatic drugs dilate the pupil of the eye, and miotics constrict or diminish pupillary size. Drugs can render blood more coagulable or less coagulable; they can increase the hemoglobin content of the erythrocytes, reduce serum cholesterol, or expand blood volume.

Drugs (termed emetics) induce vomiting, whereas antiemetic drugs prevent vomiting. Diuretic drugs increase the flow of urine; expectorant drugs increase respiratory tract fluid; and cathartics or laxatives evacuate the bowel. Other drugs decrease the flow of urine, diminish body secretions, or induce constipation.

Drugs may be used to reduce pain, fever, thyroid activity, rhinitis, insomnia, gastric acidity, motion sickness, blood pressure, and mental depression. Other drugs can elevate mood, blood pressure, or activity of the endocrine glands. Drugs can combat infectious disease, destroy intestinal worms, or act as antidotes against the poisoning effects of other drugs. Drugs can assist in smoking cessation, alcohol withdrawal, or modify obsessive compulsive disorders.

Drugs are used to treat common infections, AIDS, benign prostatic hyperplasia, cancer, cardiovascular disease, asthma, glaucoma, Alzheimer's disease, and male impotence. They can protect against the rejection of transplanted tissues and organs and reduce the incidence of measles and mumps. Antineoplastic drugs provide one means of attacking the cancerous process; radioactive pharmaceuticals provide another.

Drugs may be used to diagnose diabetes, liver malfunction, tuberculosis, or pregnancy. They can replenish a body deficient in antibodies, vitamins, hormones, electrolytes, protein, enzymes, or blood. Drugs can prevent pregnancy, assist fertility, and sustain life itself.

Certainly the vast array of effective medicinal agents available today represents one of our greatest scientific accomplishments. It is difficult to conceive our civilization devoid of these remarkable and beneficial agents. Through their use, many of the diseases that have plagued humans throughout history, such as smallpox and poliomyelitis, are now virtually extinct. Illnesses such as diabetes, hypertension, and mental depression are now effectively controlled with modern drugs. Today's surgical procedures would be virtually impossible without the benefit of anesthetics, analgesics, antibiotics, blood transfusions, and intravenous fluids.

New drugs may be derived from plant or animal sources, as byproducts of microbial growth, through chemical synthesis, molecular modification, or biotechnology. Computer libraries or data banks of chemical compounds and sophisticated methods of screening for potential biological activity assist the process of drug discovery.

The process of drug discovery and development is complex. It involves the collective contributions of many scientific specialists including organic, physical, and analytical chemists, biochemists, molecular biologists, bacteriologists, physiologists, pharmacologists, toxicologists, hematologists, immunologists, endocrinologists, pathologists, biostatisticians, pharmaceutical scientists, clinical pharmacists, physicians, and many others.

After a potential new drug substance is discovered and has undergone definitive chemical and physical characterization, a great deal of biological information must be gathered. The basic pharmacology or the nature and mechanism of action of the drug on the biological system must be determined including toxicologic features. A study must be made of the drug's site and rate of absorption, its pattern of distribution and concentration within the body, its duration of action, and the method and rate of its elimination or excretion. Information must be obtained on the drug's metabolic degradation and the activity of any of its metabolites. A comprehensive study must be made of the short-term and long-term effects of the drug on various body cells, tissues, and organs. Highly specific information may be obtained, as the effect of the drug on the fetus of a pregnant animal or its ability to pass to a nursing baby through the breast milk of its mother. Many a promising new drug has been abandoned because of its potential to cause excessive or hazardous adverse effects.

The most effective routes of administration (e.g., oral, rectal, parenteral) must be determined, and guidelines have to be established concerning the dosages recommended for persons of varying ages (e.g., neonates, children, adults, geriatrics), weights, and states of illness. To facilitate administration of the drug by the selected routes, appropriate dosage forms as tablets, capsules, injections, suppositories, ointments, aerosols, and others are formulated and prepared. Each of these dosage units is designed to contain a specified quantity of medication for ease and accuracy of dosage administration. These dosage forms are highly sophisticated pharmaceutical drug delivery systems. Their design, development, production, and utilization represent the application of the pharmaceutical sciences—the blending of the basic, applied, and clinical sciences with pharmaceutical technology.

Each particular pharmaceutical product is a formulation unique unto itself. In addition to the active therapeutic ingredients, a pharmaceutical formulation also contains a number of nontherapeutic or pharmaceutic ingredients. It is through their use that a formulation achieves its unique composition and characteristic physical appearance. Pharmaceutic ingredients include such materials as fillers, thickeners, solvents, suspending agents, tablet coatings and disintegrants, stabilizing agents, antimicrobial preservatives, flavors, colorants, and sweeteners.

To ensure the stability of a drug in a formulation and the continued effectiveness of the drug prod-

uct throughout its usual shelf life, the principles of chemistry, physical pharmacy, microbiology, and pharmaceutical technology must be applied. The formulation must be such that all components are physically and chemically compatible, including the active therapeutic agents, the pharmaceutic ingredients, and the packaging materials. The formulation must be preserved against decomposition due to chemical degradation and protected from microbial contamination and the destructive influences of excessive heat, light, and moisture. The therapeutic ingredients must be released from the dosage form in the proper quantity and in such a manner that the onset and duration of the drug's action is that which is desired. The pharmaceutical product must lend itself to efficient administration and must possess attractive features of flavor, odor, color, and texture that enhance patient acceptance. Finally, the product must be effectively packaged and clearly and completely labeled according to existing legal regulations.

Once prepared, the pharmaceutical product must be properly administered if the patient is to receive maximum benefit. The medication must be taken in sufficient quantity, at specified intervals, and for an indicated duration of time to achieve the desired therapeutic outcomes. The effectiveness of the medication in achieving the prescriber's objectives should be reevaluated at regular intervals and necessary adjustments made in the dosage, dosage regimen or dosage schedule, dosage form, or indeed, in the choice of the drug administered. Patient expressions of disappointment in his or her rate of progress or complaints of side effects to the prescribed drug should be evaluated and decisions made as to the continuance, adjustment, or major change in drug therapy. Before initially taking a medication, a patient should be advised of any expected side effects, and of foods, beverages, and/or other drugs that may interfere with the effectiveness of the medication.

Through professional interaction and communication with other health professionals the pharmacist is able to contribute greatly to patient care. An intimate knowledge of drug actions, pharmacotherapeutics, formulation and dosage form design, available pharmaceutical products, and drug information sources makes the pharmacist a vital member of the health care team. The pharmacist is entrusted with the legal responsibility for the procurement, storage, control, and distribution of effective pharmaceutical products and for the compounding and filling of prescription orders. Utilizing extensive training and knowledge, the pharmacist serves the patient as an advisor on drugs and encourages their safe and proper utilization. The pharmacist delivers pharmaceutical services in a variety of community and institutional health care environments and effectively utilizes medication records, patient monitoring, and assessment techniques in safeguarding the public health.

To appreciate the progress that has been made in drug discovery and development and to provide background for the study of modern drugs and pharmaceutical dosage forms, it is important to examine pharmacy's heritage.

The Heritage of Pharmacy

Drugs, in the form of vegetation and minerals, have existed longer than humans. Human disease and the instinct to survive have, through the ages, led to their discovery. The use of drugs, crude though they may have been, undoubtedly dates back long before recorded history, for the instinct of primitive man to relieve the pain of a wound by bathing it in cool water or by soothing it with a fresh leaf or protecting it with mud is within the realm of belief. From experience, primitive humans would learn that certain therapy was more effective than others, and from these beginnings, came the practice of drug therapy.

Among many early races, disease was believed to be caused by the entrance of demons or evil spirits into the body. The treatment naturally involved ridding the body of the supernatural intruders. From the earliest records, the primary methods of removing spirits were through the use of spiritual incantations, the application of noisome materials, and the administration of specific herbs or plant materials.

The First Apothecary

Before the days of the priestcraft, the wise man or woman of the tribe, whose knowledge of the healing qualities of plants had been gathered through experience or handed down by word of mouth, was called upon to attend to the sick or wounded and prepare the remedy. It was in the preparation of the medicinal materials that the art of the apothecary originated.

The art of the apothecary has always been associated with the mysterious, and its practitioners were believed to have connection with the world of spirits and thus performed as intermediaries between the seen and the unseen. The belief that a

drug had magical associations meant that its action, for good or for evil, did not depend upon its natural qualities alone. The compassion of a god, the observance of ceremonies, the absence of evil spirits, and the healing intent of the dispenser were individually and collectively needed to make the drug therapeutically effective. Because of this, the tribal apothecary was one to be feared, respected, trusted, sometimes mistrusted, worshiped, and revered, for it was through his potions that spiritual contact was made and upon which the cures or failures depended.

Throughout history, the knowledge of drugs and their application to disease has always meant power. In the Homeric epics, the term pharmakon (Gr.) from which our word pharmacy was derived connotes a charm or a drug that can be used for good or for evil purposes. Many of the tribal apothecary's failures were doubtless due to impotent or inappropriate medicines, underdosage, overdosage, and even poisoning. Successes may be attributed to experience, mere coincidence of appropriate drug selection, natural healing, inconsequential effect of the drug, or placebo effects, successful treatment due to psychologic rather than therapeutic effects. Even today, placebo therapy with nonpotent or inconsequential chemicals is used successfully to treat individual patients and is a routine practice in the clinical evaluation of new drugs, in which subjects' responses to the effects of the actual drug and the placebo are compared and evaluated.

As time passed, the art of the apothecary became combined with priestly functions, and among the early civilizations, the priest-magician or priest-physician became the healer of the body as well as of the soul. Pharmacy and medicine are indistinguishable in their early history because their practice was the combined function of the tribal religious leaders.

Early Drugs

Due to the patience and intellect of the archeologist, the types and specific drugs used in the early history of drug therapy are not as indefinable as one might suspect. Numerous ancient tablets, scrolls, and other relics dating as far back as 3000 BC have been uncovered and deciphered by archaeologic scholars to the delight of historians of both medicine and pharmacy; these ancient documents are specific associations with our common heritage (Fig. 1.1).

Perhaps the most famous of these surviving memorials is the Papyrus Ebers, a continuous scroll

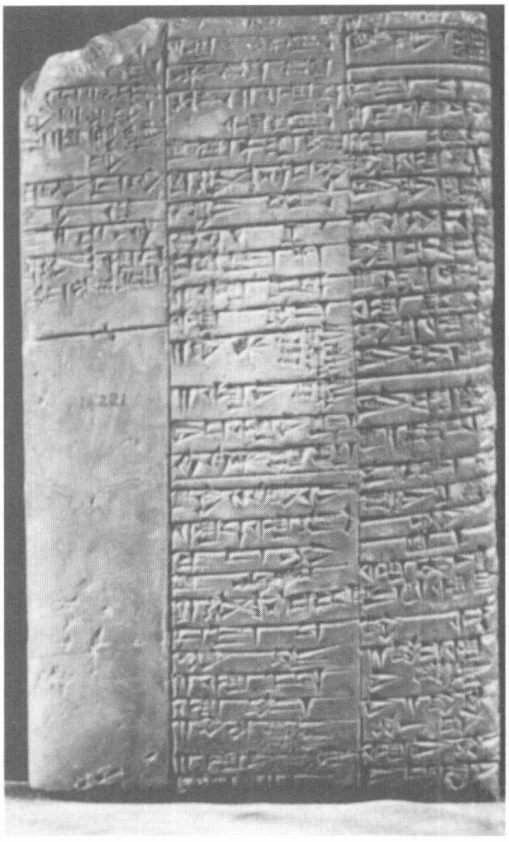


Fig. 1.1 *Sumerian clay tablet from the third millennium* BC *on which are believed to be the world's oldest written prescriptions. Among them are a preparation of the seed of "carpenter plant," gum resin of markhazi, and thyme, all pulverized and dissolved in beer, and a combination of powdered roots of "Moon plant," and white pear tree, also dissolved in beer. (Courtesy of the University Museum, University of Pennsylvania.)*

some 60 feet long and a foot wide dating back to the 16th century before Christ. This document, which is now preserved at the University of Leipzig, is named for the noted German Egyptologist, Georg Ebers, who discovered it in the tomb of a mummy and partly translated it during the last half of the nineteenth century. Since that time, many scholars have participated in the translation of the document's challenging hieroglyphics, and although they are not unanimous in their interpretations, there is little doubt that by 1550 BC, the Egyptians were using some drugs and dosage forms that are still used today.

The text of the Ebers Papyrus is dominated by drug formulas, with more than 800 formulas or prescriptions being described and over 700 different drugs being mentioned. The drugs referred to are

chiefly botanic, although mineral and animal drugs are also noted. Such botanic substances as acacia, castor bean (from which we express castor oil), and fennel are mentioned along with apparent references to such minerals as iron oxide, sodium carbonate, sodium chloride, and sulfur. Animal excrements were also used in drug therapy.

The formulative vehicles of the day were beer, wine, milk, and honey. Many of the pharmaceutical formulas employed two dozen or more different medicinal agents, a type of preparation later referred to as a "polypharmacal." Mortars, hand mills, sieves, and balances were commonly used by the Egyptians in their compounding of suppositories, gargles, pills, inhalations, troches, lotions, ointments, plasters, and enemas.

Introduction of the Scientific Viewpoint

Throughout history, many individuals have contributed to the advancement of the health sciences. Notable among those whose genius and creativeness had a revolutionary influence on the development of pharmacy and medicine were Hippocrates (ca. 460–377 BC), Dioscorides (1st century AD), Galen (ca. 130–200 AD), and Paracelsus (1493–1541 AD).

Hippocrates was a Greek physician who is credited with the introduction of scientific pharmacy and medicine. He rationalized medicine, systematized medical knowledge, and put the practice of medicine on a high ethical plane. His thinking on the ethics and science of medicine dominated the medical writings of his and successive generations, and his concepts and precepts are embodied into the now renowned Hippocratic Oath of ethical behavior for the healing professions. His works included the descriptions of hundreds of drugs, and it was during this period that the term pharmakon came to mean a purifying remedy for good only, transcending the previous connotation of a charm or drug for good or for evil purposes. Because of his pioneering work in medical science and his inspirational teachings and advanced philosophies that have become a part of modern medicine, Hippocrates is honored by being called the "Father of Medicine."

Dioscorides, a Greek physician and botanist, was the first to deal with botany as an applied science of pharmacy. His work, De Materia Medica, is considered a milestone in the development of pharmaceutical botany and in the study of naturally occurring medicinal materials. This area of study is today known as pharmacognosy, a term formed from two Greek words, *pharmakon,* drug, and *gnosis,* knowledge. Some of the drugs described by Dioscorides, as opium, ergot, and hyoscyamus, continue to have use in medicine. His descriptions of the art of identifying and collecting natural drug products, the methods of their proper storage, and the means of detecting adulterants or contaminants were the standards of the period, established the need for additional work, and set guidelines for future investigators.

Claudius Galen, a Greek pharmacist-physician who attained Roman citizenship, aimed to create a perfect system of physiology, pathology, and treatment and formulated doctrines that were followed for 1500 years. He was one of the most prolific authors of his or any other era, having been credited with 500 treatises on medicine and some 250 others on subjects of philosophy, law, and grammar. His medical writings include descriptions of numerous drugs of natural origin with a profusion of drug formulas and methods of compounding. He originated so many preparations of vegetable drugs by mixing or melting the individual ingredients that the area of pharmaceutical preparations was once commonly referred to as "Galenic pharmacy." Perhaps the most famous of his formulas is one for a cold cream, called Galen's Cerate, which has similarities to some in use today.

Pharmacy remained a function of medicine until the increasing variety of drugs and the growing complexity of compounding demanded specialists who could devote full attention to the art. Pharmacy was officially separated from medicine for the first time in 1240 AD when a decree of the German Emperor Frederick II regulated the practice of pharmacy within that part of his kingdom called the Two Sicilies. His edict separating the two professions acknowledged that pharmacy required special knowledge, skill, initiative, and responsibility if adequate care to the medical needs of the people was to be guaranteed. Pharmacists were obligated by oath to prepare reliable drugs of uniform quality according to their art. Any exploitation of the patient through business relations between the pharmacist and the physician was strictly forbidden. Between that time and the evolution of chemistry as an exact science, pharmacy and chemistry became united as pharmacy and medicine had been.

Perhaps no person in history exercised such a revolutionary influence on pharmacy and medicine as did Aureolus Philippus Theophrastus Bombastus von Hohenheim, a Swiss physician and chemist who called himself Paracelsus. He influenced the

transformation of pharmacy from a profession based primarily on botanic science to one based on chemical science. Some of his chemical observations were astounding for his time and for their anticipation of later discoveries. He believed it was possible to prepare a specific medicinal agent to combat each specific disease and introduced a host of chemical substances to internal therapy.

Early Research

As the knowledge of the basic sciences increased, so did their application to pharmacy. The opportunity was presented for the investigation of medicinal materials on a firm scientific basis, and the challenge was accepted by numerous pharmacists who conducted their research in the back rooms and basements of their pharmacies. Noteworthy among them was Karl Wilhelm Scheele (1742–1786), a Swedish pharmacist who is perhaps the most famous of all pharmacists because of his scientific genius and dramatic discoveries. Among his discoveries were the chemicals lactic acid, citric acid, oxalic acid, tartaric acid, and arsenic acid. He identified glycerin, invented new methods of preparing calomel and benzoic acid, and discovered oxygen a year before Priestley.

The isolation of morphine from opium by the German pharmacist Friedrich Sertürner (1783–1841) in 1805 prompted a series of isolations of other active materials from medicinal plants by a score of French pharmacists. Joseph Caventou (1795–1877) and Joseph Pelletier (1788–1842) combined their talents and isolated quinine and cinchonine from cinchona, and strychnine and brucine from nux vomica. Pelletier together with Pierre Robiquet (1780–1840) isolated caffeine, and Robiquet independently separated codeine from opium. Methodically one chemical after another was isolated from plant drugs and identified as an agent responsible for the plants' medicinal activity. Today we are still engaged in this fascinating activity as we probe nature for more useful and more specific therapeutic agents. Contemporary examples of drugs isolated from a natural source include paclitaxel (Taxol), an agent with antitumor activity derived from the Pacific yew tree (Taxus baccata) and employed in the treatment of metastatic carcinoma of the ovary; vincaleukoblastine, another antineoplastic drug, from Vinca rosea; and digoxin, a cardiac glycoside, from Digitalis lanata.

Throughout Europe during the late 18th century and the beginning of the 19th century, pharmacists like Pelletier and Sertürner were held in great esteem because of their intellect and technical abilities. They applied the art and the science of pharmacy to the preparation of drug products that were of the highest standards of purity, uniformity, and efficacy possible at that time. The extraction and isolation of active constituents from crude (unprocessed) botanic drugs led to the development of dosage forms of uniform strength containing singly effective therapeutic agents of natural origin. Many pharmacists of the period began to manufacture quality pharmaceutical products on a small but steadily increasing scale to meet the growing drug needs of their communities. Some of today's largest pharmaceutical research and manufacturing companies developed from these progressive prescription laboratories of two centuries ago.

Although many of the drugs indigenous to America and first used by the American Indian were adopted by the settlers, the vast majority of drugs needed in this country before the 19th century were imported from Europe, either as the raw materials or as finished pharmaceutical products. With the Revolutionary War, however, it became more difficult to import drugs, and the American pharmacist was stimulated to acquire the scientific and technologic expertise of his European contemporary. From this period until the Civil War, pharmaceutical manufacture was in its infancy in this country. A few of the pharmaceutical firms established during the early 1800s are still in operation. In 1821, the Philadelphia College of Pharmacy was established as the nation's first school of pharmacy.

Drug Standards

As the scientific basis for drugs and drug products developed, so did the need for uniform standards to ensure quality. This need led to the development and publication of monographs and reference books containing such standards to be utilized by those involved in the production of drugs and pharmaceutical products. Organized sets of monographs or books of these standards are referred to as "pharmacopeias" or "formularies."

The United States Pharmacopeia and The National Formulary

The term pharmacopeia comes from the Greek, *pharmakon,* meaning "drug," and *poiein,* meaning "make," and the combination indicates any recipe or formula or other standards required to make or prepare a drug. The term was first used in 1580 in connection with a local book of drug standards in Berg-

amo, Italy. From that time on there were countless city, state, and national pharmacopeias published by various European pharmaceutical societies. As time passed, the value of a uniform set of national drug standards became apparent. In England, for example, three city pharmacopeias—the London, the Edinburgh, and the Dublin—were official throughout the kingdom until 1864, when they were replaced by the British Pharmacopoeia (BP).

In the United States, drug standards were first provided on a national basis in 1820, when the first United States Pharmacopeia (USP) was published. However, the need for drug standards was recognized in this country long before the first USP was published. For convenience and because of their familiarity with them, colonial physicians and apothecaries used the pharmacopeias and other references of their various homelands. The first American pharmacopeia was the so-called "Lititz Pharmacopeia," published in 1778 at Lititz, Pennsylvania, for use by the Military Hospital of the United States Army. It was a 32-page booklet containing information on 84 internal and 16 external drugs and preparations.

During the last decade of the 18th century, several attempts were made by various local medical societies to collate drug information, set appropriate standards, and prepare an extensive American pharmacopeia of the drugs in use at that time. In 1808, the Massachusetts Medical Society published a 272-page pharmacopeia containing information or monographs on 536 drugs and pharmaceutical preparations. Included were monographs on many drugs indigenous to America, which were not described in the European pharmacopeias of the day.

On January 6, 1817, Dr. Lyman Spalding, a physician from New York City, submitted a plan to the Medical Society of the County of New York for the creation of a national pharmacopeia. Dr. Spalding's efforts were later to result in his being recognized as the "Father of the United States Pharmacopeia." He proposed dividing the United States as then known into four geographic districts—Northern, Middle, Southern, and Western. The plan provided for a convention in each of these districts, to be composed of delegates from all medical societies and medical schools within them. Where there was as yet no incorporated medical society or medical school, voluntary associations of physicians and surgeons were invited to assist in the undertaking. Each district's convention was to draft a pharmacopeia and appoint delegates to a general convention to be held later in Washington, D.C. At the general convention, the four district pharmacopeias were to be compiled into a single national pharmacopeia.

Draft pharmacopeias were submitted to the convention by only the Northern and Middle districts. These were reviewed, consolidated, and adopted by the first United States Pharmacopeial Convention assembled in Washington, D.C., on January 1, 1820. The first United States Pharmacopeia (USP) was published on December 15, 1820, in English and also in Latin, then the international language of medicine, to render the book more intelligible to physicians and pharmacists of any nationality. Within its 272 pages were listed 217 drugs considered worthy of recognition; many of them were taken from the Massachusetts Pharmacopeia, which is considered by some to be the precursor to the USP. The objective of the first USP was stated in its preface and remains important. It reads in part: (1)

> It is the object of a Pharmacopeia to select from among substances which possess medicinal power, those, the utility of which is most fully established and best understood; and to form from them preparations and compositions, in which their powers may be exerted to the greatest advantage. It should likewise distinguish those articles by convenient and definite names, such as may prevent trouble or uncertainty in the intercourse of physicians and apothecaries.

Before adjourning, the Convention adopted a Constitution and Bylaws, with provisions for subsequent meetings of the Convention leading to a revised United States Pharmacopeia every 10 years. As many new drugs entered into drug therapy, the need for more frequent issuance of standards became increasingly apparent. In 1900, the Pharmacopeial Convention granted authority to issue supplements to the currently official USP whenever necessary to maintain satisfactory standards. At the 1940 meeting of the Convention, it was decided to revise the Pharmacopeia every 5 years while maintaining the use of periodic supplements.

The first United States Pharmacopeial Convention was composed exclusively of physicians. In 1830, and again in 1840, prominent pharmacists were invited to assist in the revision, and recognition of their contributions pharmacists were awarded full membership in the Convention of 1850 and have participated regularly ever since. By 1870, the Pharmacopeia was so nearly in the hands of pharmacists that vigorous efforts were required to revive interest in it among physicians. The present Constitution and Bylaws of The United States Pharmacopeial Convention provide for accredited delegates representing educational institutions,

professional and scientific organizations, divisions of governmental bodies, non-United States international organizations and pharmacopeial bodies, persons who possess special scientific competence or knowledge of emerging technologies, and public members.(3) Of the seven elected members of the Board of Trustees, at least two must be representatives of the medical sciences, two others must be representatives of the pharmaceutical sciences, and at least one must be a public member.

After the appearance of the first USP, the art and science of both pharmacy and medicine changed remarkably. Before 1820, drugs to treat disease were the same for centuries. The Pharmacopeia of 1820 reflected the fact that the apothecary of that day was competent at collecting and identifying botanic drugs and preparing from them the mixtures and preparations required by the physician. The individual pharmacist seemed fulfilled as he applied his total art to the creation of elegant pharmaceutical preparations from crude botanic materials. It was a time that would never be seen again because of the impending upsurge in technologic capabilities and the steady development of the basic sciences, particularly synthetic organic chemistry.

The second half of the 19th century brought great and far-reaching changes. The United States was now under the full impact of the industrial revolution. The steam engine, which used water power to turn mills that powdered crude botanic drugs, was replaced by the gas, diesel, or electric motor. New machinery was substituted for the old whenever possible, and often machinery from other industries was adapted to the special needs of pharmaceutical manufacturing. Mixers from the baking industry, centrifugal machines from the laundry industry, and sugarcoating pans from the candy industry were a few examples of the type of improvisations made. Production increased rapidly, but the new industry had to wait for the scientific revolution before it could claim newer and better drugs for mankind. A symbiosis was needed between science and the advancing technology.

By 1880, the industrial manufacture of chemicals and pharmaceutical products had become well established in this country, and the pharmacist was relying heavily on commercial sources for drug supply. Synthetic organic chemistry began to have its influence on drug therapy. The isolation of some active constituents of plant drugs had led to knowledge of their chemical structure. From this arose methods of synthetically duplicating the same structures, as well as manipulating molecular structure to produce organic chemicals yet undiscovered in nature. In 1872, the synthesis of salicylic acid from phenol inaugurated the synthesis of a group of analgesic compounds including acetylsalicylic acid (aspirin), which was introduced into medicine in 1899. Among other chemicals synthesized for the first time were sleep-producing derivatives of barbituric acid called "barbiturates." This new source of drugs—synthetic organic chemistry—welcomed the turn into the 20th century.

Until this time, drugs created through the genius of the synthetic organic chemist relieved a host of maladies, but none had been found to be curative—none, that is, until 1910, when arsphenamine, a specific agent against syphilis, was introduced to medical science. This was the start of an era of chemotherapy, an era in which the diseases of humans became curable through the use of specific chemical agents. The concepts, discoveries, and inspirational work that led mankind to this glorious period are credited to Paul Ehrlich, the German bacteriologist who together with a Japanese colleague, Sahachiro Hata, discovered arsphenamine. Today most of our new drugs, whether they are curative or palliative, originate in the flask of the synthetic organic chemist.

The advancement of science, both basic and applied, led to drugs of a more complex nature and to more of them. The drug standards advanced by the USP were more than ever needed to protect the public by ensuring the purity and uniformity of the drugs administered.

When the American Pharmaceutical Association (APhA) was organized in 1852, the only authoritative and recognized book of drug standards available was the third revision of the United States Pharmacopeia. To serve as a therapeutic guide to the medical profession, its scope, then as now, was restricted to drugs of established therapeutic merit. Because of strict selectivity, many drugs and formulas that were accepted and used by the medical profession were not granted admission to early revisions of the Pharmacopeia. As a type of a protest, and in keeping with the original objectives of the American Pharmaceutical Association to establish standardization of drugs and formulas, certain pharmacists, with the sanction of their national organization, prepared a formulary containing many of the popular drugs and formulas denied admission to the Pharmacopeia. The first edition was published in 1888 under the title National Formulary of Unofficial Preparations. The designation Unofficial Preparations reflected the protest mood of the authors, since the Pharmacopeia had earlier adopted the term "official" as applying to the drugs for which it provided standards. The title was changed to National Formulary (NF) on June 30, 1906 when Pres-

ident Theodore Roosevelt signed into law the first federal Pure Food and Drug Act, designating both the USP and NF as establishing legal standards for medicinal and pharmaceutic substances. Thus the two publications became official compendia. Among other things, the law required that whenever the designations "USP" or "NF" were used or implied on drug labeling, the products must conform to the physical and chemical standards set forth in the compendium monograph.

The early editions of the National Formulary served mainly as a convenience to practicing pharmacists by providing uniform names of drugs and preparations and working directions for the small-scale manufacture of popular pharmaceutical preparations prescribed by physicians. Before 1940, the NF, as the USP, was revised every 10 years. After that date, new editions appeared every 5 years, with supplements issued periodically as necessary.

In 1975, the United States Pharmacopeial Convention, Inc. purchased the National Formulary, unifying the official compendia and thereby provided the mechanism for a single, national compendium.

The first combined compendium, representing the USPXX and NFXV became official on July 1, 1980. All monographs on therapeutically active drug substances appeared in the USP section of the volume, whereas all monographs on pharmaceutic agents appeared in the NF section. This format has been continued in subsequent revisions. The United States Pharmacopeia 23/National Formulary 18, which became official in 1995 was the first edition to drop the use of roman numerals in favor of arabic numerals to indicate the edition. The most recent edition of the USP-NF contains over 3,400 drug monographs and is published both in print and on CD-ROM.

The standards advanced by the United States Pharmacopeia and the National Formulary are put to active use by all members of the health care industry who share the responsibility and enjoy the public's trust for assuring the availability of quality drugs and pharmaceutical products. Included in this group are pharmacists, physicians, dentists, veterinarians, nurses, producers, and suppliers of bulk chemicals for use in drug production, large and small manufacturers of pharmaceutical products, drug procurement officers of various private and public health agencies and institutions, drug regulatory and enforcement agencies, and others.

USP and NF Monographs

The United States Pharmacopeia and the National Formulary adopt standards for drug substances, pharmaceutic ingredients, and dosage forms reflecting the best in the current practices of medicine and pharmacy and provide suitable tests and assay procedures for demonstrating compliance with these standards. In fulfilling this function, the compendia become legal documents, every statement of which must be of a high degree of clarity and specificity.

Many pharmaceutical products on the market, especially those which are combinations of therapeutic ingredients, are not represented by formulation or dosage form monographs in the official compendia. However, the individual components in these products are either represented by monographs in the compendia, in supplements to the compendia, or in drug applications for marketing approved by the Food and Drug Administration.

An example of a typical monograph for a drug substance appearing in the USP is shown in Figure 1.2. This monograph demonstrates the type of information that appears for organic medicinal agents.

The initial part of the monograph consists of the official title (generic or nonproprietary name) of the drug substance. This is followed by its graphic or structural formula, its empirical formula, molecular weight, established chemical names, and the drug's Chemical Abstracts Service (CAS) Registry Number. The CAS Registry Number identifies each compound uniquely in the CAS computer-oriented information retrieval system. Appearing next in the monograph is a statement of chemical purity, a cautionary statement that reflects the toxic nature of the agent, packaging and storage recommendations, and chemical and physical tests and the prescribed method of assay to substantiate the identification and purity of the chemical.

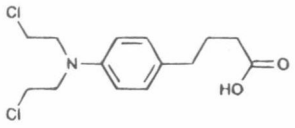
In each monograph, the standards set forth are specific to the individual therapeutic agent, pharmaceutic material, or dosage form preparation to assure purity, potency, and quality.

The USP Drug Research and Testing Laboratory provides direct laboratory assistance to the United States Pharmacopeia and the National Formulary. The Laboratory's main functions are the evaluation of USP Reference Standards and the evaluation and development of analytical methods to be used in the compendia.

Other Pharmacopeias

In addition to the USP and the NF, other references to drug standards such as the Homeopathic Pharmacopeia of the United States (HPUS) and the International Pharmacopeia (IP) provide additional

Chlorambucil



$C_{14}H_{19}Cl_2NO_2$ 304.22 Benzenebutanoic acid, 4-[bis(2-chloroethyl)amino]-4-[*p*[Bis(2-chloroethyl)amino] phenyl]butyric acid [*305-03-3*].

▸ Chlorambucil contains not less than 98.0% and not more than 101.0% of $C_{14}H_{19}Cl_2NO_2$, calculated on the anhydrous basis.

Caution—Great care should be taken to prevent inhaling particles of Chlorambucil and exposing the skin to it.

Packaging and storage—Preserve in tight, light-resistant containers.

Reference standard—*USP Chlorambucil Reference Standard—[Caution—Avoid contact]*—Dry over silica gel for 24 hours before using.

Identification—

A: The infrared absorption spectrum of a 1 in 125 solution in carbon disulfide, in a 1-mm cell, exhibits maxima only at the same wavelengths as that of a similar solution of USP Chlorambucil RS.

B: Dissolve 50 mg in 5 mL of acetone, and dilute with water to 10 mL. Add 1 drop of 2 *N* sulfuric acid, then add 4 drops of silver nitrate TS: no opalescence is observed immediately *(absence of chloride ion)*. Warm the solution on a steam bath: opalescence develops *(presence of ionizable chlorine)*.

Melting range (741): between 65° and 69°.

Water, *Method I* (921): not more than 0.5%.

Assay—Dissolve about 200 mg of Chlorambucil, accurately weighed, in 10 mL of acetone, add 10 mL of water, and titrate with 0.1 *N* sodium hydroxide VS, using phenolphthalein TS as the indicator. Each mL of 0.1 *N* sodium hydroxide is equivalent to 30.42 mg of $C_{14}H_{19}Cl_2NO_2$.

Fig. 1.2 *Chlorambucil.*

guidelines for drug quality required by certain practitioners and agencies. The Homeopathic Pharmacopeia is used by pharmacists and homeopathists as well as by law enforcement agencies that must ensure the quality of homeopathic drugs. The term homeopathy was coined by Samuel Hahnemann (1755–1843) from the Greek homoios, meaning similar, and pathos, meaning disease. In essence, the basic tenet of homeopathy is the "law of similars" or that like cures like: that is, a drug that produces symptoms of the illness in healthy persons will also be capable of treating those same symptoms and curing the disease. Embodied in the homeopathic approach are 1) the testing of a drug on healthy persons to find the drug's effects so that it may be employed against the same symptoms manifesting a disease in an ill person, 2) the use of only minute doses of drugs in therapy, employed in dilutions expressed as "1x" (a 1:10 dilution), "2x" (a 1:100 dilution), etc., 3) the administration of not more than one drug at a time, and 4) the treatment of the entire symptom complex of the patient, not just one symptom (4–6). The Homeopathic Pharmacopeia is essential for pharmacists who prepare drugs to be used in the practice of homeopathy.

The Pharmacopeia Internationalis, or International Pharmacopeia is published by the World Health Organization (WHO) of the United Nations with the cooperation of member countries. It is intended as a recommendation to national pharmacopeial revision committees to modify their respective pharmacopeias according to the international standards adopted. It has no legal authority, only the mutual respect and recognition accorded it by the participating countries in their effort to provide acceptable drug standards on an international basis. The first volume of the Pharmacopeia Internationalis was published in 1951. It has been revised periodically since that time.

Over the years, a number of countries have published their own pharmacopeias, including Great Britain, France, Italy, Japan, India, Mexico, Norway, and the former Union of Soviet Socialist Republics. These pharmacopeias and the European Pharmacopeia (EP or Ph Eur) are used within the respective legal jurisdictions and by multinational pharmaceutical companies that develop and market products internationally. Countries not having a national pharmacopeia frequently adopt one of another country in setting and regulating drug standards. The pharmacopeia selected is usually based on geographic proximity, a common heritage or language, or a similarity of drugs and pharmaceutical products used. For example, Canada, which does not have its own national pharmacopeia, has traditionally used USP/NF standards. The Mexican Pharmacopeia [Farmacopea de los Estados Unidos Mexicanos (FEUM)] is the only other actively maintained pharmacopeia in this hemisphere (7).