

Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems

E I G H T H E D I T I O N



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CELGENE 2065
APOTEX v. CELGENE
IPR2023-00512

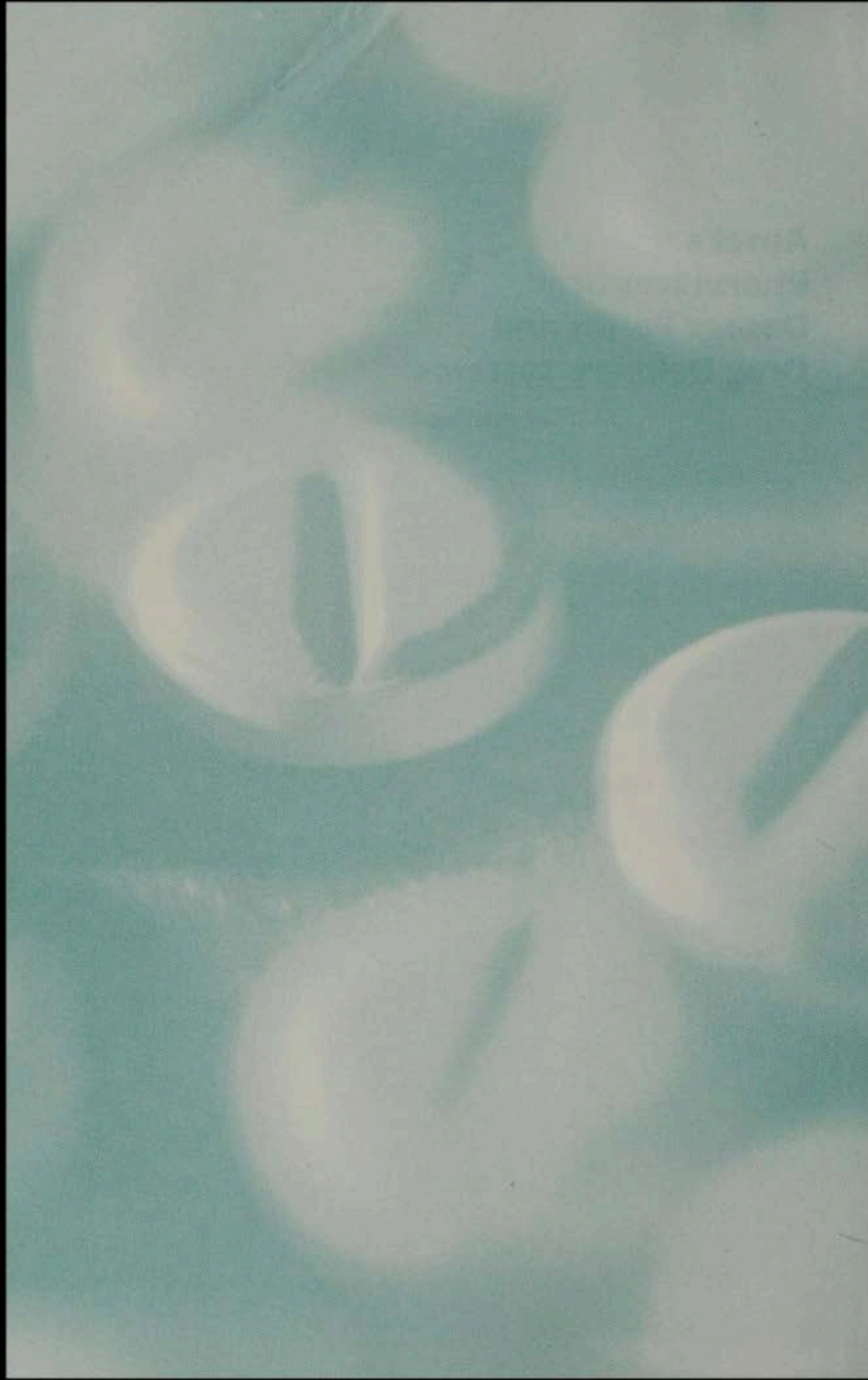


LIPPINCOTT WILLIAMS & WILKINS



**Ansel's
Pharmaceutical
Dosage Forms and
Drug Delivery Systems**

EIGHTH EDITION



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Senior Acquisitions Editor: David B. Troy
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Production Editor: Jennifer Ajello
Designer: Doug Smock
Compositor: Peirce Graphic Services, LLC
Printer: Data Reproductions Corp.

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Baltimore, MD 21201

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Printed in the United States of America

Library of Congress Cataloging-in-Publication Data

Allen, Loyd V.

Ansel's pharmaceutical dosage forms and drug delivery systems / Loyd V. Allen Jr., Nicholas G. Popovich, Howard C. Ansel.—8th ed.

p. ; cm.

Rev. Ed. of: *Pharmaceutical dosage forms and drug delivery systems* / Howard C. Ansel, Loyd V. Allen, Jr., Nicholas G. Popovich. 7th ed. c1999.

Includes bibliographical references and index.

ISBN 0-7817-4612-4

1. Drugs—Dosage forms. 2. Drug delivery systems. I. Title: *Pharmaceutical dosage forms and drug delivery systems*. II. Popovich, Nicholas G. III. Ansel, Howard C., 1933– IV. Ansel, Howard C., 1933– *Pharmaceutical dosage forms and drug delivery systems*. V. Title.

[DNLM: 1. Dosage Forms. 2. Drug Delivery Systems. QV 785 A427a2004]

RS200.A57 2004

615'.1—dc22

2004048276

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Preface

The purpose of this text is to introduce pharmacy students to the principles and technologies applied in the preparation of pharmaceutical dosage forms and drug delivery systems. An integrated presentation is used to demonstrate the interrelationships between pharmaceutical and biopharmaceutical principles, product design, formulation, manufacture, and the clinical application of the various dosage forms in patient care. Regulations governing the manufacturing and compounding of pharmaceuticals are also presented.

As has been the hallmark of this textbook since its first edition more than 30 years ago, each chapter is written at a level consistent with the requirements of students being introduced to this area of study. Because this textbook often is used early in the professional curriculum, it contains important introductory topics, such 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, pharmaceutical and biopharmaceutical 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 Eighth Edition

The eighth edition presents a significant rewrite of some of the sections of the previous edition. We have reorganized the book into eight divisions, containing 20 chapters, based upon traditional pharmaceutical 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 continue to emphasize important underlying pharmaceutical principles. Also continued in this edition is the Chapter at a Glance at the beginning of each chapter.

Other important changes:

- Enhanced considerations of dosage form design and formulation
- Two case studies (one pharmaceutical and one clinical) in each of the dosage form chapters (see "Introduction to the SOAP Format for Case Studies," next)
- An update of the current good compounding practices
- Expanded clinical considerations in the use of the dosage forms
- Two new glossaries in the appendix, one listing dosage forms and one listing pharmaceutical terms, back as a result of numerous requests of students and faculty.

Introduction to the SOAP Format for Case Studies^a

The most commonly used documentation format for case studies is referred to by the mnemonic SOAP, which stands for Subjective information, Objective information, Assessment, and Plan.

^aAdapted with permission from O'Sullivan TA, Wittkowsky AK. Clinical drug monitoring. In Boh LE, ed. *Pharmacy Practice Manual: A Guide to the Clinical Experience*, 2nd ed. Baltimore: Lippincott Williams & Wilkins, 2001:594.

The content of a SOAP note written by a pharmacist will be slightly different from that written by another type of health care provider, primarily in the assessment section; a pharmacist's SOAP note will primarily identify problems of diagnosis.

Before a SOAP note is begun, the following must be clearly defined:

- What are the patient's most important problems that must be addressed and/or resolved now?
- What is the evidence that each problem exists?
- What are the therapeutic goals and options for each problem?

The answers to each of these questions will form the content of the assessment section of the SOAP note. Therefore, the assessment is written mentally before the actual SOAP note is begun. After the problems are defined, subjective and objective information needed to justify why those problems exist should be written down.

The first paragraph begins with "S:" and contains subjective information, which is obtained from the patient interview. Examples of subjective information include patient-provided information about disease symptoms, over-the-counter medications, drug allergy descriptions, and compliance.

The second paragraph begins with "O:" and contains objective information obtained by physically examining the patient, reading laboratory data, checking prescription records for doses and refill patterns, locating medication costs from a printed or on-line formulary, and so on. Some information can be either subjective or objective, depending on how it is obtained. The most important thing to remember when composing the subjective and objective portions of notes is that *only information pertaining directly to the assessment should be included.*

The third paragraph begins with "A:" and contains the pharmacist's assessment of the patient's medical and pharmacologic problem or problems. If the subjective and objective paragraphs are written well, the problem should be obvious to the reader. Other types of information included in the assessment paragraph are the therapeutic goals and a brief discussion of the therapeutic alternatives.

The fourth paragraph begins with either "P:" or "R:" and details either a plan (P), or recommendation (R), whichever is more appropriate for the situation. The plan should include individualized instructions (drug by generic name, dose, route, frequency, and when applicable, duration of therapy). The exact dose and frequency should be identified.

Also, the monitoring plan must be detailed, including specifically what (e.g., laboratory test, symptom) should be measured, who should measure it (patient, caregiver, pharmacist), when and how frequently the measuring should occur, and at what point changing therapy will be considered. A backup plan for use in the event of therapeutic failure should also be noted here. Finally, instructions for the proper use of prescribed medication or medications should be included to enhance the therapeutic outcome.

Acknowledgments

I acknowledge with grateful appreciation the major contributions and foresight of Howard C. Ansel, the originator of the textbook, whose guidance and hard work over the years have significantly contributed to the education of tens of thousands of pharmacists worldwide. Deep appreciation to Nicholas G. Popovich for his extensive contribution to this textbook in clinical pharmacy and pharmacy practice and his unique ability to present the integrated approach used in this work. Together, we extend our gratitude to students and academic colleagues who have shared their thoughts with us on this revision; we hope that we have been successful in responding to their thoughtful suggestions. We also acknowledge with appreciation our colleagues in industry who have generously provided scientific and technical information and updated figures and photos for our use.

We gratefully acknowledge the following individuals who contributed to the development of this book through their critiques, review, and suggestions of the individual chapters. Chapter 15 (Parenterals): Jane A. Gottlieb, RPh; David Donley RPh, Manager of the Pharmacy Department at Clarian Health, Indianapolis, Indiana; and Mary Baker, PharmD, MBA, Senior Medical Manager, Global Medical Affairs, Hospira, Inc. Chapter 16 (Biologics): Mary Ann Kliethermes, PharmD, Pharmacotherapist, Clinical Assistant Professor of the Ambulatory Care Pharmacy and Manager of the Refill-10 Program of the Pharmaceutical Care Center; and Leslie Ann Briars, PharmD, Clinical Assistant Professor and Pediatric Clinical Pharmacist of Ambulatory Care Pharmacy Services at the University of Illinois at Chicago, College of Pharmacy. Chapter 18 (Radiopharmaceuticals): Dan Murphy, RPh, Regional Pharmacy Compliance Specialist, West Hartford, Connecticut; Peter Sposato, RPh, Pharmacy Manager at Syncor International Corporation, Glastonbury, Connecticut; and Louis Juliano, RPh, Senior Director of Operations, Northeast at the Cardinal Health Nuclear Pharmacy Services, Kings Park, New York. In addition, we thank the following former doctoral students at the University of Illinois at Chicago College of Pharmacy and Purdue University School of Pharmacy and Pharmacal Sciences for their critiques, review, and suggestions of the individual chapters. They are Raoof R. Abdellatif, PharmD; Nancy J. Costlow, PharmD; Paul S. Djuricich, PharmD; Huzefa H. Master, PharmD; Mary E. Kiersma, PharmD; and Jennifer Thomas, PharmD.

New to this edition are the dosage form chapter case studies. A number of former doctoral students at the University of Illinois at Chicago College of Pharmacy and the Purdue University School of Pharmacy and Pharmacal Sciences prepared the clinical case studies, and we sincerely appreciate their contribution to the text. Those participating and the chapters in which their cases appear are as follows: Chapters 6 and 9, Yamini Shah, PharmD; Chapters 7 and 8, Sumi Patel, PharmD; Chapters 10 and 11, Rebecca L. Roche, PharmD; Chapter 12, Malisa H. Patel, PharmD; Chapter 13, Kristin M. Hurt, PharmD; Chapters 14 and 17, Kristin M. Hurt PharmD and Malisa H. Patel, PharmD; Chapter 15, Natalie Y. Vazzana, PharmD, and Elizabeth Chu, PharmD; and Chapters 16 and 19, James Song, PharmD. Nicki L. Hilliard, PharmD, MSHA, BCNP, FAPhA, Associate Professor of Nuclear Pharmacy at the University of Arkansas College of Pharmacy, created the clinical case for Chapter 18.

We especially thank the staff at Lippincott Williams & Wilkins who have contributed so expertly to the planning, preparation, and production of this new edition: David Troy, Matt Hauber, Samantha Smith, and Jennifer Ajello.

LOYD V. ALLEN, JR.
Edmond, Oklahoma

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Glossary of Pharmaceutical Terms

Appendix B

- Active Ingredient:** the ingredient or ingredients of a pharmaceutical product responsible for its pharmacologic activity (also medicament, drug substance, active pharmaceutical ingredient).
- Aerosol:** a dosage form that is packaged under pressure and contains therapeutically active ingredients that are released upon activation of an appropriate valve system.
- Ampul:** a final container that is all glass in which the open end, after filling with product, is sealed by heat (also ampoule, ampule, [French] carpule).
- Aseptic:** lacking disease-producing microorganisms; not the same as sterile.
- Aseptic Processing:** manufacturing dosage forms without terminal sterilization. The dosage form is sterile-filtered, then aseptically filled into the final package and aseptically sealed.
- Bead:** a solid dosage form in the shape of a small sphere. The dosage form generally contains multiple beads (also pellet).
- Bolus:** a large, long tablet intended for administration to animals.
- Capsule:** a solid dosage form in which the drug is enclosed within a hard or soft soluble container or shell.
- Capsule, Delayed-release:** a coated capsule or more commonly encapsulated granules that may be coated to resist releasing the drug in the stomach because the drug will irritate gastric mucosa or gastric fluid will inactivate the drug.
- Capsule, Extended-release:** a capsule that is formulated in such a manner as to make the contained medication available over an extended period following ingestion.
- Capsule, Soft-shell:** a solid dosage form in which one or more active ingredients, normally in solution or suspension or in the form of a paste, is filled into a one-piece shell.
- Collodion:** a liquid preparation composed of pyroxilin dissolved in a solvent mixture of alcohol and ether and applied externally.
- Concentrate for Dip:** a preparation containing one or more active ingredients usually in the form of a paste or solution; it is used to prepare a diluted suspension, emulsion, or solution of the active ingredient(s) for the prevention and treatment of ectoparasitic infestations of animals.
- Cream:** a semisolid dosage form containing one or more drug substances dissolved or dispersed in a suitable base.
- Drops, Oral:** a solution, emulsion, or suspension that is administered in small volumes, such as drops, by means of a suitable device.
- Effervescent:** a dosage form containing ingredients that rapidly release carbon dioxide when in contact with water.
- Elixir:** a clear, pleasantly flavored, sweetened hydroalcoholic liquid containing dissolved active ingredients intended for oral use.
- Emulsion:** a two-phase system in which one liquid is dispersed throughout another liquid in the form of small droplets.
- Excipient:** an inactive ingredient of a dosage form.
- Extract:** a concentrated preparation of vegetable or animal drug obtained by removal of the active constituents with suitable menstrua, by evaporation of all or nearly all of the solvent and by adjustment of the residual mass or powder to the prescribed standards.
- Fluidextract:** a liquid preparation of a vegetable drug containing alcohol as a solvent, preservative, or both and so made that unless otherwise specified in an individual monograph, each milliliter contains the therapeutic constituents of 1 g of the standard drug.
- Foam:** an emulsion packaged in a pressurized aerosol container that has a fluffy, semisolid consistency when dispensed.
- Gel:** a semisolid system consisting of either a suspension of small inorganic particles or large organic molecules interpenetrated by a liquid.
- Granules:** a preparation of dry aggregates of powder particles that may contain one or more active ingredients with or without other ingredients.
- Implant:** see pellet; a small sterile solid mass consisting of a highly purified drug with or without excipients made by compression or molding and put in place by injection or incision.
- Infusion, Intramammary:** a suspension of a drug in a suitable oil vehicle; intended for veterinary use only.

- Inhalation:** a solution or suspension of one or more drug substances administered by the nasal or oral respiratory route for local or systemic effect.
- Injection:** a preparation intended for parenteral administration or for constituting or diluting a parenteral article prior to administration.
- Irrigation:** a sterile solution intended to bathe or flush open wounds or body cavities.
- Jelly:** see gel.
- Liniment:** an alcoholic or oleaginous solution or emulsion applied by rubbing on the skin for treating pain and stiffness of underlying musculature.
- Lotion:** a fluid suspension or emulsion applied to the surface of the skin. See solution or suspension.
- Lozenge:** a solid preparation that is intended to dissolve or disintegrate slowly in the mouth.
- Lyophilization:** removal of water or other solvent from a frozen solution by sublimation caused by a combination of temperature and pressure differentials (also freeze drying).
- Modified Release:** a release pattern of the active ingredient from the dosage form that has been deliberately changed from that of the conventional form. Includes accelerated release, delayed release, extended release, pulsatile release, targeted release, and so on.
- Molded Tablet:** a tablet that has been formed by dampening the ingredients and pressing them into a mold, then removing and drying the resulting solid mass.
- Mouthwash:** an aqueous solution used to rinse the oral cavity.
- Ointment:** a semisolid preparation intended for external application to the skin or mucous membrane.
- Ophthalmic Preparation:** drug in dosage form intended to be applied to the eye.
- Ophthalmic Ointment:** a sterile ointment intended for application to the eye.
- Ophthalmic Solution:** a sterile solution, essentially free from foreign particles, suitably prepared and packaged for instillation into the eye.
- Ophthalmic Suspension:** a sterile liquid preparation containing solid particles dispersed in a liquid vehicle intended for application to the eye.
- Ophthalmic Strip:** a sterile single-use container or sterile impregnated paper strip containing the drug to be applied to the eye.
- Orally Disintegrating:** a solid oral dosage form that disintegrates rapidly in the mouth to facilitate release of the active ingredient.
- Otic Solution:** a solution intended for instillation in the outer ear.
- Otic Suspension:** a liquid preparation containing micronized particles intended for instillation in the outer ear.
- Paste:** a semisolid dosage form that contains one or more drug substances intended for topical application. It generally contains a high concentration of solids and has a stiff consistency.
- Pellet:** see bead. (Also a solid granule or regular shape prepared by compaction or by granulation.)
- Pill:** a solid spherical dosage form, usually prepared by a wet massing technique.
- Plaster:** a solid or semisolid mass supplied on a backing material and intended to provide prolonged contact with the skin.
- Powder:** an intimate mixture of dry, finely divided drug and/or chemicals that may be intended for internal (oral) or external (topical) use.
- Premix:** a mixture of one or more drug substances with a suitable vehicle.
- Pulsatile Release:** a release pattern of the active ingredient from the dosage form that is modified to release aliquots of the total dose at two or more time intervals.
- Rinse:** a solution used to cleanse by flushing.
- Shampoo:** a solution, emulsion, or suspension used to clean the hair and scalp.
- Soap:** the alkali salt(s) of one or more fatty acids.
- Solution:** a liquid preparation that contains one or more dissolved (molecularly dispersed) chemical substances in a suitable solvent or mixture of miscible solvents; may be oral, topical, otic, ophthalmic.
- Spirit:** an alcoholic or hydroalcoholic solution of volatile substances prepared usually by simple solution or by admixture of the ingredients.
- Sterile:** completely lacking living (viable) microbial life.
- Sterility:** an acceptably high level of probability that a product processed in an aseptic system does not contain viable microorganisms.
- Stick:** a slender, cylindrical dosage form of rigid consistency.
- Suppository:** a solid body adapted for introduction into the rectal, vaginal, or urethral orifice.
- Suppository Tablet or Insert:** a vaginal suppository prepared by compression of powdered materials into a suitable shape; can also be prepared by encapsulation in soft gelatin.
- Suspension:** a liquid preparation that consists of solid particles dispersed throughout a liquid phase in which the particles are not soluble; may be oral, topical, otic ophthalmic.
- Syrup:** a solution containing a high concentration of sucrose or other sugars. See solution.
- System:** a dosage form developed to allow for uniform release or targeting of drugs to the body.
- System, Transdermal:** a self-contained, discrete

- dosage form that is designed to deliver drug(s) through the intact skin to the systemic circulation.
- System, Ocular:** a dosage form intended for placement in the lower conjunctival fornix, from which the drug diffuses through a membrane at a constant rate.
- System, Intrauterine:** a system that is intended for release of drug over a long period, such as a year.
- Tablet:** a solid dosage form containing medicinal substance(s) with or without diluents.
- Tablet, Chewable:** a tablet formulated so that it may be chewed, producing a pleasant-tasting residue that is easily swallowed and does not leave a bitter or unpleasant aftertaste.
- Tablet, Delayed-release:** a tablet with a coating that is intended to postpone release of the medication until the tablet has passed through the stomach.
- Tablet, Extended-release:** a tablet that is formulated so as to make the contained medication available over an extended period following ingestion.
- Targeted Release:** release of the active ingredient from a dosage form modified to preferentially deliver most of the drug to a specific region, organ, or tissue.
- Terminal Sterilization:** a process used to produce sterility in a final product contained in its final packaging system.
- Tincture:** an alcoholic or hydroalcoholic solution prepared from vegetable materials or from chemical substances.
- Transdermal Delivery System, Electroporation:** a transdermal delivery system enhanced by the application of short, high-voltage electric pulses to create aqueous pores in the lipid bilayer of skin and thereby facilitate drug diffusion.
- Transdermal Delivery System, High Velocity Powder Particles:** a transdermal drug delivery system using supersonic shock waves of helium gas to enhance drug diffusion through the skin.
- Transdermal Delivery System, Iontophoresis:** a transdermal drug delivery system enhanced by the use of applied electric current to facilitate drug diffusion through the skin.
- Transdermal Delivery System, Phonophoresis:** a transdermal drug delivery system enhanced by the application of low-frequency ultrasound to facilitate drug diffusion through the skin (also ultrasound, sonophoresis, ultrasonophoresis, ultraphonophoresis).
- Transdermal Matrix Patch:** a transdermal matrix system using a polymeric matrix containing drug intended for systemic delivery through the skin; generally the skin is the rate-controlling membrane for drug diffusion.
- Transdermal Membrane Patch:** a transdermal system containing a drug reservoir entrapped between backing and adhesive layers and a drug diffusion-controlling membrane; the reservoir is usually a semisolid dispersion or solution of the drug.
- Troche:** see lozenge.
- Urethral:** a dosage form intended for insertion into the urethra to provide a local effect of the active ingredient.
- Validation:** scientific study to prove that a process is doing what it is supposed to do and is under control.
- Water, Aromatic:** a clear, saturated aqueous solution (unless otherwise specified) of one or more volatile oils or other aromatic or volatile substances.