

Remington
The Science and Practice
of Pharmacy

Nineteenth Edition

Volume I

Remington: The Science and Practice of Pharmacy

Volume I

19TH
EDITION

Remington: Practice of

ALFONSO R GENNARO

*Chairman of the Editorial Board
and Editor*

The Science and Pharmacy

1995

MACK PUBLISHING COMPANY
Easton, Pennsylvania 18042

Entered according to Act of Congress, in the year 1885 by Joseph P Remington,
in the Office of the Librarian of Congress, at Washington DC

Copyright 1889, 1894, 1905, 1907, 1917, by Joseph P Remington

Copyright 1926, 1936, by the Joseph P Remington Estate

Copyright 1948, 1951, by The Philadelphia College of Pharmacy and Science

Copyright 1956, 1960, 1965, 1970, 1975, 1980, 1985, 1990, 1995, by The Philadelphia College of
Pharmacy and Science

All Rights Reserved

Library of Congress Catalog Card No. 60-53334

ISBN 0-912734-04-3

*The use of structural formulas from USAN and the USP Dictionary of Drug Names is by
permission of The USP Convention. The Convention is not responsible for any inaccuracy
contained herein.*

*NOTICE—This text is not intended to represent, nor shall it be interpreted to be, the equivalent
of or a substitute for the official United States Pharmacopeia (USP) and / or the National
Formulary (NF). In the event of any difference or discrepancy between the current official
USP or NF standards of strength, quality, purity, packaging and labeling for drugs and
representations of them herein, the context and effect of the official compendia shall prevail.*

Printed in the United States of America by the Mack Printing Company, Easton, Pennsylvania

Remington: The Science and Practice of Pharmacy . . . *a treatise on the theory and practice of the pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also a guide to the professional responsibilities of the pharmacist as the drug-information specialist of the health team . . . A textbook and reference work for pharmacists, physicians and other practitioners of the pharmaceutical and medical sciences.*

EDITORS

Alfonso R Gennaro, <i>Chairman</i>	Thomas Medwick
Grafton D Chase	Edward G Rippie
Ara Der Marderosian	Joseph B Schwartz
Glen R Hanson	H Steve White
Daniel A Hussar	Gilbert L Zink

AUTHORS

The 112 chapters of this edition of *Remington* were written by the editors, by members of the Editorial Board, and by other authors listed on pages x to xii.

Managing Editor

John E Hoover, BSc (Pharm)

Editorial Assistant

Bonnie Brigham Packer, RNC, BA

Director

Allen Misher 1985–1995

Nineteenth Edition—1995

Published in the 175th year of the
PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE

Remington Historical/Biographical Data

The following is a record of the editors and the dates of publication of successive editions of this book, prior to the 13th Edition known as *Remington's Practice of Pharmacy* and subsequently as *Remington's Pharmaceutical Sciences* through the 18th Edition.

First Edition, 1886
Second Edition, 1889
Third Edition, 1897
Fourth Edition, 1905

Joseph P Remington

Fifth Edition, 1907
Sixth Edition, 1917

Joseph P Remington
Assisted by
 E Fullerton Cook

Seventh Edition, 1926

Editors
 E Fullerton Cook
 Charles H LaWall

Eighth Edition, 1936

Editors
 E Fullerton Cook
 Charles H LaWall

Associate Editors
 Ivor Griffith
 Adley B Nichols
 Arthur Osol

Ninth Edition, 1948
Tenth Edition, 1951

Editors
 E Fullerton Cook
 Eric W Martin

Eleventh Edition, 1956

Editors
 Eric W Martin
 E Fullerton Cook

Associate Editors
 E Emerson Leuallen
 Arthur Osol
 Linwood F Tice
 Clarence T Van Meter

Twelfth Edition, 1961

Editors
 Eric W Martin
 E Fullerton Cook
 E Emerson Leuallen
 Arthur Osol
 Linwood F Tice
 Clarence T Van Meter

Assistant to the Editors
 John E Hoover

Thirteenth Edition, 1965

Editor-in-Chief
 Eric W Martin
Editors
 Grafton D Chase
 Herald R Cox
 Richard A Deno
 Alfonso R Gennaro
 Stewart C Harvey

Managing Editor
 John E Hoover

Robert E King
 E Emerson Leuallen
 Arthur Osol
 Ewart A Swinyard
 Clarence T Van Meter

Fourteenth Edition, 1970

Chairman, Editorial Board
 Arthur Osol

Editors
 Grafton D Chase
 Richard A Deno
 Alfonso R Gennaro
 Melvin R Gibson
 Stewart C Harvey

Managing Editor
 John E Hoover

Robert E King
 Alfred N Martin
 Ewart A Swinyard
 Clarence T Van Meter

Fifteenth Edition, 1975

Chairman, Editorial Board
 Arthur Osol

Editors
 John T Anderson
 Cecil L Bendush
 Grafton D Chase
 Alfonso R Gennaro
 Melvin R Gibson

Managing Editor
 John E Hoover

C Boyd Granberg
 Stewart C Harvey
 Robert E King
 Alfred N Martin
 Ewart A Swinyard

Sixteenth Edition, 1980

Chairman, Editorial Board
 Arthur Osol

Editors
 Grafton D Chase
 Alfonso R Gennaro
 Melvin R Gibson

C Boyd Granberg
 Stewart C Harvey
 Robert E King
 Alfred N Martin
 Ewart A Swinyard
 Gilbert L Zink

Seventeenth Edition, 1985

Chairman, Editorial Board
 Alfonso R Gennaro

Editors
 Grafton D Chase
 Ara Der Marderosian
 Stewart C Harvey
 Daniel A Hussar
 Thomas Medwick

Edward G Rippie
 Joseph D Schwartz
 Ewart A Swinyard
 Gilbert L Zink

Eighteenth Edition, 1990

Chairman, Editorial Board
 Alfonso R Gennaro

Editors
 Grafton D Chase
 Ara Der Marderosian
 Stewart C Harvey
 Daniel A Hussar
 Thomas Medwick

Managing Editor
 John E Hoover
Editorial Assistant
 Bonnie Packer

Edward G Rippie
 Joseph D Schwartz
 Ewart A Swinyard
 Gilbert L Zink

Editorial Board Members and Editors

Alfonso R Gennaro, PhD / *Philadelphia College of Pharmacy and Science*—Professor of Chemistry. Chairman of the Editorial Board and Editor, *Remington: The Science and Practice of Pharmacy*. Coeditor of Part 6, *Pharmaceutical and Medicinal Agents*. Coauthor of Chapter 24.

Grafton D Chase, PhD* / *Philadelphia College of Pharmacy and Science*—Emeritus Professor of Chemistry, Editorial Board Member. Coauthor of Chapters 25 and 51.

Ara DerMarderosian, PhD / *Philadelphia College of Pharmacy and Science*—Professor of Pharmacognosy. Research Professor of Medicinal Chemistry. Editor of Part 1, *Orientation*. Author of Chapters 49, 78 and 99. Coauthor of Chapter 50.

Glen R Hanson, DDS, PhD / *University of Utah College of Pharmacy*—Professor of Pharmacology and Toxicology. Editorial Board Member. Coeditor of Part 5, *Pharmacodynamics* and Part 6, *Pharmaceutical and Medicinal Agents*. Author of Chapters 56, 62, 63, 68, 69 and 72. Coauthor of Chapter 40.

Daniel A Hussar, PhD / *Philadelphia College of Pharmacy and Science*—Remington Professor of Pharmacy. Editorial Board Member. Editor of Part 8, *Pharmacy Practice*. Author of Chapters 103 and 105.

Thomas Medwick, PhD / *Rutgers University College of Pharmacy*—Professor of Pharmaceutical Chemistry and Director, Graduate Program in Pharmaceutical Sciences. Editorial Board Member. Editor of Part 3, *Pharmaceutical Chemistry*, and Part 4, *Testing, Analysis and Control*. Coauthor of Chapters 23 and 29.

Edward G Rippie, PhD / *University of Minnesota College of Pharmacy*—Professor of Pharmaceutics. Editorial Board Member. Editor of Part 2, *Pharmaceutics*. Author of Chapter 12. Coauthor of Chapter 91.

Joseph D Schwartz, PhD / *Philadelphia College of Pharmacy and Science*—Burroughs Wellcome Professor of Pharmaceutics. Editorial Board Member. Editor of Part 7, *Industrial Pharmacy*. Coauthor of Chapters 91 and 92.

H Steve White, PhD / *University of Utah College of Pharmacy*—Research Assistant Professor of Pharmacology and Toxicology. Coeditor of Part 5, *Pharmacodynamics* and Part 6, *Pharmaceutical and Medicinal Agents*. Author of Chapters 61, 70, 73 and 77. Coauthor of Chapter 40.

Gilbert L Zink, PhD / *Philadelphia College of Pharmacy and Science*—Associate Professor of Biology. Editorial Board Member. Editor of Chapters 44, 81 and 82. Author of Chapter 44.

*Deceased.

Authors

The following contributors to the Nineteenth Edition of *Remington* served as authors or coauthors, along with the editors and members of the Editorial Board, of the 112 chapters of this book.

- Hamed M Abdou, PhD** / Vice President, Worldwide Pharmaceutical Technical Operations, Bristol-Myers Squibb Company, Inc; Author of Chapter 33, *Instrumental Methods of Analysis* and Chapter 34, *Dissolution*.
- Ann B Amerson, PharmD** / Professor, College of Pharmacy and Director, Drug Information Center, Chandler Medical Center, University of Kentucky; Author of Chapter 106, *Clinical Drug Literature*.
- Howard C Ansel, PhD** / Professor of Pharmaceutics, College of Pharmacy, University of Georgia; Author of Chapter 104, *The Prescription*.
- Michael A Ashburn, MD** / Associate Professor of Anesthesiology, School of Medicine, University of Utah; Author of Chapter 67, *General Anesthetic Drugs*.
- Kenneth E Avis, DSc** / Emeritus Professor, Pharmaceutics, College of Pharmacy, University of Tennessee, Memphis; Coauthor of Chapter 87, *Parenteral Preparations*.
- Leonard C Bailey, PhD** / Professor of Pharmaceutical Chemistry, Rutgers University College of Pharmacy; Author of Chapter 32, *Chromatography*.
- Jan N Bair, PhD** / Associate Professor of Hospital Pharmacy, Director of Pharmacy Services, University of Utah Hospital; Author of Chapter 79, *Diagnostic Agents*.
- Louis R. Barrows, PhD** / Associate Professor of Pharmacology and Toxicology, College of Pharmacy, University of Utah; Author of Chapter 75, *Antineoplastic and Immunoactive Drugs*.
- Lawrence H Block, PhD** / Professor of Pharmaceutics, Duquesne University School of Pharmacy; Author of Chapter 90, *Medicated Applications*.
- Joseph B Bogardus, PhD** / Director, Pharmaceutics Research and Development, Bristol-Myers Squibb Company; Coauthor of Chapter 18, *Reaction Kinetics*.
- Sanford Bolton, PhD** / Chairman, Department of Pharmacy and Administrative Sciences, St. John's University; Author of Chapter 10, *Statistics*.
- B Sue Brizuela, MS** / Account Representative, Chemical Abstracts Service; Coauthor of Chapter 7, *Drug Information*.
- Karleen S Callahan, PhD** / Research Assistant Professor of Pharmacology and Toxicology, College of Pharmacy, University of Utah; Author of Chapter 54, *Blood, Fluids, Electrolytes and Hematologic Drugs*.
- Charles S Chiao, PhD** / Andia SR Pharmaceuticals Inc; Coauthor of Chapter 94, *Sustained-Release Drug Delivery Systems*.
- Dale B Christensen, PhD** / Associate Professor, Department of Pharmacy, School of Pharmacy, University of Washington; Coauthor of Chapter 11, *Computer Science*.
- Kenneth A Connors, PhD** / Professor of Pharmaceutics, School of Pharmacy, University of Wisconsin; Author of Chapter 14, *Complex Formation*.
- Anthony R DiSanto, PhD** / Pharmaceutical Consultant; Author of Chapter 35, *Bioavailability and Bioequivalency Testing*.
- Clarence A Discher,* PhD** / Professor Emeritus, Rutgers University; Coauthor of Chapter 23, *Inorganic Pharmaceutical Chemistry*.
- Clyde R Erskine, Jr, BSc** / Vice President (Retired) Worldwide Quality Assurance, SmithKline Beecham Corporation; Coauthor of Chapter 39, *Quality Assurance and Control*.
- William E Fassett, BS, MBA** / Associate Professor and Chair, College of Pharmacy and Health Sciences, Department of Pharmacy, Drake University; Coauthor of Chapter 11, *Computer Science*.
- Joseph L Fink III, BS(Pharm), JD** / Associate Vice Chancellor for Academic Affairs, University of Kentucky; Coauthor of Chapter 110, *Laws Governing Pharmacy*.
- Michael R Franklin, PhD** / Professor of Pharmacology, College of Pharmacy and School of Medicine, University of Utah; Author of Chapter 41, *Drug Absorption, Action and Disposition* and Chapter 66, *Enzymes*.
- Donald R Franz, PhD** / Professor of Pharmacology, School of Medicine, University of Utah; Author of Chapter 55, *Cardiovascular Drugs*; Chapter 57, *Sympathomimetic Drugs*; Chapter 58, *Cholinomimetic Drugs*; Chapter 59, *Adrenergic and Adrenergic Neuron Blocking Drugs* and Chapter 60, *Antimuscarinic and Antispasmodic Drugs*.
- Ruta Freimanis, PharmD** / Secretary, United States Adopted Names Council; Coauthor of Chapter 27, *Drug Nomenclature—United States Adopted Names*.
- Raymond Galinsky, PharmD** / Associate Professor of Pharmaceutics and Pharmaceutical Chemistry, College of Pharmacy, University of Utah; Coauthor of Chapter 42, *Basic Pharmacokinetics*.
- Barry Garfinkle, PhD** / Executive Director, Quality Operations, Merck Sharpe & Dohme; Coauthor of Chapter 84, *Sterilization*.
- Harold N Godwin, MS** / Professor and Director of Pharmacy, The University of Kansas Medical Center; Author of Chapter 97, *Institutional Patient Care*.
- Frederick J Goldstein, PhD** / Professor of Pharmacology, Philadelphia College of Osteopathic Medicine; Author of Chapter 47, *Pharmacological Aspects of Drug Abuse*.
- Abraham Haddad, PhD** / Vice President for Administration, Massachusetts College of Pharmacy and Allied Health Sciences; Author of Chapter 1, *Scope*.
- Gerald Hecht, PhD** / Senior Director, Alcon Laboratories; Author of Chapter 89, *Ophthalmic Preparations*.
- Martin Henley, PhD** / Associate Director, Sterile Process Engineering, Merck Sharpe & Dohme; Coauthor of Chapter 84, *Sterilization*.
- Karl A Herzog, PhD** / Pharmaceutical Industry Consultant; Director Quality Assurance US Bioscience (Retired); Coauthor of Chapter 39, *Quality Assurance and Control*.
- Judith A Hesp, MS** / Manager of Education Services, Scott Memorial Library, Thomas Jefferson University; Coauthor of Chapter 7, *Drug Information*.
- Gregory J Higby, PhD** / Director, American Institute of the History of Pharmacy, School of Pharmacy, University of Wisconsin-Madison; Author of Chapter 2, *Evolution of Pharmacy*.
- Andrew S Katocks, Jr, PhD** / Senior Research Pharmacologist, American Cyanamid Company, Medical Research Division; Author of Chapter 30, *Biological Testing*.
- Russ Katz, MD** / Deputy Director of New Line, Division of Neuropharmacological Drug Products, Food and Drug Administration; Author of Chapter 48, *Introduction of New Drugs*.
- Calvin H Knowlton, MDiv, PhD** / Associate Professor of Pharmacy, Philadelphia College of Pharmacy and Science; Author of Chapter 4, *Community Pharmacy*.
- Richard W Kneuppel, RPh** / President, Kneuppel Home Health Care Center; Author of Chapter 107, *Health Accessories*.
- Kristine Knutson, PhD** / Associate Professor of Pharmaceutics, College of Pharmacy, University of Utah; Coauthor of Chapter 52, *Topical Drugs*.
- Harry B Kostenbauder, PhD** / Emeritus Professor, College of Pharmacy, University of Kentucky; Coauthor of Chapter 18, *Reaction Kinetics*.

*Deceased

- Allen M Kratz, PharmD** / President, HOBON Inc; Coauthor of Chapter 50, *Alternative Healthcare*.
- Arthur J Lawrence, PhD** / Office of the Assistant Secretary of Health, US Public Health Service; Author of Chapter 6, *Pharmacists in Government*.
- John W Levchuk, PhD** / Adjunct Associate Professor of Pharmaceutics, College of Pharmacy, University of Maryland; Coauthor of Chapter 87, *Parenteral Preparations*.
- Eric J Lien, PhD** / Professor of Pharmacy/Pharmaceutics and Biomedical Chemistry, School of Pharmacy, University of Southern California; Author of Chapter 13, *Molecular Structure, Properties and States of Matter*.
- Karen B Main, PhD** / Group Leader, Pharmaceutical Development Department, Zeneca Pharmaceuticals Group; Coauthor of Chapter 29, *Analysis of Medicinals*.
- Anthony S Manoguerra, PharmD** / Professor of Clinical Pharmacy, Director, San Diego Regional Poison Center, UCSD Medical Center; Coauthor of Chapter 109, *Poison Control*.
- William F McGhan, PharmD, PhD** / Professor of Pharmacy, Department of Pharmacy Practice, Philadelphia College of Pharmacy and Science; Author of Chapter 112, *Pharmacoconomics*.
- Duane D Miller, PhD** / Van Vleet Professor, Department of Pharmaceutical Sciences, College of Pharmacy, The Ohio State University; Author of Chapter 28, *Structure-Activity Relationship and Drug Design*.
- Michael Montagne, PhD** / Associate Professor of Social Pharmacy, Massachusetts College of Pharmacy & Allied Health Sciences; Coauthor of Chapter 3, *Ethics* and Author of Chapter 102, *Drug Education*.
- Maven J Myers, PhD** / Professor of Pharmacy Administration, Philadelphia College of Pharmacy and Science; Coauthor of Chapter 3, *Ethics*.
- J G Nairn, PhD** / Professor of Pharmacy, Faculty of Pharmacy, University of Toronto; Author of Chapter 86, *Solutions, Emulsions, Suspensions and Extracts*.
- William K Nichols, PhD** / Associate Professor of Pharmacology, College of Pharmacy, University of Utah; Author of Chapter 64, *Hormones* and Chapter 76, *Anti-Infective Drugs*.
- Paul J Niebergall, PhD** / Professor of Pharmaceutical Sciences/Director, Pharmaceutical Development Center, Medical University of South Carolina; Author of Chapter 17, *Ionic Solutions and Electrolytic Equilibria*.
- Robert E O'Connor, PhD** / The R W Johnson Pharmaceutical Research Institute; Coauthor of Chapter 91, *Powders*.
- Garnet E Peck, PhD** / Professor of Industrial Pharmacy/Director of the Industrial Pharmacy Laboratory, Purdue University; Author of Chapter 37, *Separation*.
- Chris Perigard, BS, MT(ASCP), MBA** / Clinical Pathologist, Pharmaceutical Research Institute, Bristol-Myers Squibb Company; Coauthor of Chapter 31, *Clinical Analysis*.
- Lynn K Pershing, PhD** / Research Associate Professor of Internal Medicine, School of Medicine, University of Utah; Coauthor of Chapter 52, *Topical Drugs*.
- Nicholas G Popovich, PhD** / Professor of Pharmacy Practice, School of Pharmacy and Pharmaceutical Sciences, Purdue University; Author of Chapter 96, *Ambulatory Patient Care*.
- Stuart C Porter, PhD** / Vice President, Research and Development, Colorcon; Author of Chapter 93, *Coating of Pharmaceutical Dosage Forms*.
- Barrett E Rabinow, PhD** / Director, Strategic Development, Baxter Healthcare Corporation; Coauthor of Chapter 85, *Plastic Packaging Materials*.
- Galen Radebaugh, PhD** / Director of Pharmaceutics, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company; Coauthor of Chapter 83, *Preformulation*.
- Paul L Ranelli, PhD** / Assistant Professor of Pharmacy and Health Care Administration, College of Pharmacy, University of Florida; Author of Chapter 101, *Patient Communication*.
- Louis J Ravin, PhD** / Pharmaceutical Consultant; Coauthor of Chapter 83, *Preformulation*.
- Irwin Reich, BSc(Pharm)** / Instructor and Manager of the Pharmacy Laboratory, Philadelphia College of Pharmacy and Science; Coauthor of Chapter 9, *Metrology and Calculation* and Chapter 36, *Tonicity, Osmoticity, Osmolality and Osmolarity*.
- Jack W Reich, PhD** / Vice President Regulatory Affairs, Gensia Pharmaceuticals, Inc; Author of Chapter 8, *Research*.
- William Reilly, Jr, BSc(Pharm)** / Manager, Technical Services, FMC Corporation, Pharmaceutical and Bioscience Division; Author of Chapter 80, *Pharmaceutical Necessities*.
- Joseph E Rice, PhD** / Assistant Professor of Medicinal Chemistry, Department of Pharmaceutical Chemistry, Rutgers University; Coauthor of Chapter 24, *Organic Pharmaceutical Chemistry*.
- James W Richards, MBA** / Professor of Pharmacy Administration, College of Pharmacy, University of Michigan; Author of Chapter 111, *Community Pharmacy Economics and Management*.
- Jack Robbins, PhD** / Director, Pharmacy Affairs, Schering Laboratories; Author of Chapter 5, *Pharmacists in Industry*.
- Joseph R Robinson, PhD** / Professor of Pharmacy, School of Pharmacy, University of Wisconsin; Coauthor of Chapter 94, *Sustained-Release Drug Delivery Systems*.
- Frank Roia, PhD** / Professor of Biology, Philadelphia College of Pharmacy and Science; Author of Chapter 81, *Immunizing Agents and Diagnostic Skin Antigens*.
- Douglas E Rollins, MD, PhD** / Professor of Pharmacology and Toxicology, College of Pharmacy, University of Utah; Author of Chapter 43, *Clinical Pharmacokinetics*.
- Theodore J Rosemann, PhD** / Vice President for Pharmaceutical Sciences, Research and Development, Baxter Healthcare Corporation; Coauthor of Chapter 85, *Plastic Packaging Materials*.
- Edward Rudnic, PhD** / Vice President, Pharmaceutical Development, Paravene Inc; Coauthor of Chapter 92, *Oral Solid Dosage Forms*.
- Donald O Schiffman, PhD** / Emeritus Secretary, United States Adopted Names Council; Coauthor of Chapter 27, *Drug Nomenclature—United States Adopted Names*.
- Roger L Schnaare, PhD** / Professor of Pharmaceutics, Philadelphia College of Pharmacy and Science; Coauthor of Chapter 9, *Metrology and Calculation* and Chapter 36, *Tonicity, Osmoticity, Osmolality and Osmolarity*.
- Hans Schott, PhD** / Emeritus Professor of Pharmaceutics and Colloid Chemistry, School of Pharmacy, Temple University; Author of Chapter 20, *Colloidal Dispersions* and Author of Chapter 22, *Rheology*.
- Barbara Schwartz, PhD** / Vice President, New Business Development, Ethicon, Inc; Coauthor of Chapter 108, *Surgical Supplies*.
- John J Sciarra, PhD** / President, Sciarra Labs Inc/Emeritus Professor of Industrial Pharmacy, Arnold and Marie Schwartz College of Pharmacy and Health Sciences, Long Island University; Author of Chapter 95, *Aerosols*.
- Bernard Shapiro, MD** / Chairman Emeritus, Department of Nuclear Medicine, Albert Einstein Hospital, Northern Division, Philadelphia; Coauthor of Chapter 25, *Fundamentals of Radioisotopes* and Chapter 51, *Medical Applications of Radioisotopes*.
- E Richard Shough, PhD** / Associate Dean and Professor, University of Oklahoma Health Sciences Center, College of Pharmacy; Author of Chapter 82, *Allergenic Extracts*.
- Larry M Simonsmeier, BS(Pharm), JD** / Professor of Pharmacy Law, College of Pharmacy, Washington State University; Coauthor of Chapter 110, *Laws Governing Pharmacy*.
- Robert D Smyth, PhD** / Vice President, Pharmaceutical Development, Bristol-Myers Squibb Company; Coauthor of Chapter 31, *Clinical Analysis*.
- Robert J Smyth, PhD** / Department of Pharmacology, Temple University; Coauthor of Chapter 31, *Clinical Analysis*.
- Thomas C Snader, PharmD** / Consultant Pharmacist; Author of Chapter 98, *Long-Term Care Facilities*.
- Theodore D Sokoloski, PhD** / Emeritus Professor of Pharmacy, College of Pharmacy, The Ohio State University; Author of Chapter 16, *Solutions and Phase Equilibria*.
- Patricia K Sonsalla, PhD** / Assistant Professor, Department of Neurology, UMDNJ-Robert Wood Johnson Medical School; Author of Chapter 74, *Central Nervous System Stimulants*.
- Robert B Stewart, MS** / Professor, Department of Pharmacy Practice, College of Pharmacy, University of Florida; Author of Chapter 45, *Adverse Drug Reactions*.
- Edwin T Sugita, PhD** / Professor and Chair, Department of Pharmaceutics, Philadelphia College of Pharmacy and Science; Coauthor of Chapter 9, *Metrology and Calculation* and Chapter 36, *Tonicity, Osmoticity, Osmolality and Osmolarity*.

Craig K Svensson, PharmD, PhD / Associate Professor, Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, Wayne State University; Coauthor of Chapter 42, *Basic Pharmacokinetics*.

James Swarbrick, DSc, PhD / Vice President for Research and Development, AAI Inc; Author of Chapter 21, *Coarse Dispersions*.

Anthony R Temple, MD / Director, Regulatory and Medical Affairs, McNeil Consumer Products Company; Coauthor of Chapter 109, *Poison Control*.

John P Tischio, PhD / Principle Scientist, R W Johnson Research Institute; Author of Chapter 46, *Pharmacogenetics*.

Keith C Tolman, MD / Professor and Chair, Department of Gastroenterology, School of Medicine, University of Utah; Coauthor of Chapter 40, *Diseases: Manifestations and Pathophysiology* and Author of Chapter 53, *Gastrointestinal and Liver Drugs*.

Salvatore J Turco, FASHP, PharmD / Professor of Pharmacy, Temple University School of Pharmacy; Author of Chapter 88, *Intravenous Admixtures*.

Elizabeth B Vadas, PhD / Senior Director, Pharmaceutical Research and Development, Merck Frosst Canada, Inc; Author of Chapter 38, *Stability of Pharmaceutical Products*.

Ernestine Vanderveen, PhD / Director, Alcohol Research Centers Program, NIAAA; Coauthor of Chapter 65, *Vitamins and Other Nutrients*.

John E Vanderveen, PhD / Center for Food Safety and Applied Nutrition, Food and Drug Administration; Coauthor of Chapter 65, *Vitamins and Other Nutrients*.

Vincent S Venturella, PhD / Section Manager, Pharmaceutical Development, OHMEDA PPD, Division of BOC; Author of Chapter 26, *Natural Products*.

Lane Wallace, PhD / Associate Professor of Pharmacology, College of Pharmacy, Ohio State University; Author of Chapter 71, *Psychopharmacologic Agents*.

Albert I Wertheimer, PhD / Vice President, Manage Care/Pharmacy First Help Service Corporation; Author of Chapter 100, *The Patient: Behavioral Determinants*.

Timothy S Wiedmann, PhD / Assistant Professor, College of Pharmacy, University of Minnesota; Author of Chapter 15, *Thermodynamics*.

David M Wiseman, PhD / Principle Scientist, Ethicon Inc; Coauthor of Chapter 108, *Surgical Supplies*.

George Zografi, PhD / Professor, School of Pharmacy, University of Wisconsin; Author of Chapter 19, *Interfacial Phenomena*.

Preface to the First Edition

The rapid and substantial progress made in Pharmacy within the last decade has created a necessity for a work treating of the improved apparatus, the revised processes, and the recently introduced preparations of the age.

The vast advances made in theoretical and applied chemistry and physics have much to do with the development of pharmaceutical science, and these have been reflected in all the revised editions of the Pharmacopoeias which have been recently published. When the author was elected in 1874 to the chair of Theory and Practice of Pharmacy in the Philadelphia College of Pharmacy, the outlines of study which had been so carefully prepared for the classes by his eminent predecessors, Professor William Proctor, Jr, and Professor Edward Parrish, were found to be not strictly in accord, either in their arrangement of the subjects or in their method of treatment. Desiring to preserve the distinctive characteristics of each, an effort was at once made to frame a system which should embody their valuable features, embrace new subjects, and still retain that harmony of plan and proper sequence which are absolutely essential to the success of any system.

The strictly alphabetical classification of subjects which is now universally adopted by pharmacopoeias and dispensaries, although admirable in works of reference, presents an effectual stumbling block to the acquisition of pharmaceutical knowledge through systematic study; the vast accumulation of facts collected under each head arranged lexically, they necessarily have no connection with one another, and thus the saving of labor effected by considering similar groups together, and the value of the association of kindred subjects, are lost to the student. In the method of grouping the subjects which is herein adopted, the constant aim has been to arrange the latter in such a manner that the reader shall be gradually led from the consideration of elementary subjects to those which involve more advanced knowledge, whilst the groups themselves are so placed as to follow one another in a natural sequence.

The work is divided into six parts. Part I is devoted to detailed descriptions of apparatus and definitions and comments on general pharmaceutical processes.

The Official Preparations alone are considered in Part II. Due weight and prominence are thus given to the Pharmacopoeia, the National authority, which is now so thoroughly recognized.

In order to suit the convenience of pharmacists who prefer to *weigh solids* and *measure liquids*, the official formulas are expressed, in addition to parts by weight, in *avoirdupois weight* and *apothecaries' measure*. These equivalents are

printed in *bold type* near the margin, and arranged so as to fit them for quick and accurate reference.

Part III treats of Inorganic Chemical Substances. Precedence is of course given to official preparation in these. The descriptions, solubilities, and tests for identity and impurities of each substance are systematically tabulated under its proper title. It is confidently believed that by this method of arrangement the valuable descriptive features of the Pharmacopoeia will be more prominently developed, ready reference facilitated, and close study of the details rendered easy. Each chemical operation is accompanied by equations, whilst the reaction is, in addition, explained in words.

The Carbon Compounds, or Organic Chemical Substances, are considered in Part IV. These are naturally grouped according to the physical and medical properties of their principal constituents, beginning with simple bodies like cellulose, gum, etc, and progressing to the most highly organized alkaloids, etc.

Part V is devoted to Extemporaneous Pharmacy. Care has been taken to treat of the practice which would be best adapted for the needs of the many pharmacists who conduct operations upon a moderate scale, rather than for those of the few who manage very large establishments. In this, as well as in other parts of the work, operations are illustrated which are conducted by manufacturing pharmacists.

Part VI contains a formulary of Pharmaceutical Preparations which have not been recognized by the Pharmacopoeia. The recipes selected are chiefly those which have been heretofore rather difficult of access to most pharmacists, yet such as are likely to be in request. Many private formulas are embraced in the collection; and such of the preparations of the old Pharmacopoeias as have not been included in the new edition, but are still in use, have been inserted.

In conclusion, the author ventures to express the hope that the work will prove an efficient help to the pharmaceutical student as well as to the pharmacist and the physician. Although the labor has been mainly performed amidst the harassing cares of active professional duties, and perfection is known to be unattainable, no pains have been spared to discover and correct errors and omissions in the text. The author's warmest acknowledgments, are tendered to Mr A B Taylor, Mr Joseph McCreery, and Mr George M Smith for their valuable assistance in revising the proof sheets, and to the latter especially for his work on the index. The outline illustrations, by Mr John Collins, were drawn either from the actual objects or from photographs taken by the author.

Philadelphia, October, 1885

JPR.

Preface to the Nineteenth Edition

It has been the practice for the last several editions, prior to drafting a *Preface* for the forthcoming *Remington*, to reread the comments of one's predecessors. Noteworthy of almost every editor, beginning with Professor Remington himself in 1889, was the recurrent comment that the health sciences have made tremendous strides since the previous edition had appeared. It is obvious that this concept is equally valid at this writing—perhaps to an extent even greater than in any intervening revision period.

For the first time in its 110 year history, *Remington* has deviated from its customary physical form—in two ways. The immediate, discernible change is the division of the once bulky tome, the bane of every undergraduate student, into two smaller volumes. Secondly, and perhaps of more significance technologically—yet less evidently physically—is the inclusion of a Compact Disk—Read Only Memory (or CD-ROM, in the popular acronym) as a companion to the text.

This current edition also is witness to many, more subtle changes, principally in the editorial staff, authors and subject material. Firstly, the subject material from Part 3 through Part 9 (of the previous edition) has been rearranged so that a rough division into two categories could be made—a teaching or instructional segment and a supportive reference volume. The physical division into two volumes closely approximates this concept. To accomplish this end, the section dealing with *Biological Products* has been deleted and the inclusive material distributed among the two volumes as deemed necessary.

A chapter has been eliminated (*Dental Services*) with pertinent information distributed throughout the book. Several new chapters are evident such as *Alternative Medicine* (50), *Community Pharmacy Economics and Management* (111), and *Pharmacoeconomics* (112).

The number of authors has increased to 113, and of these 41 are new to this edition. As usual, the expertise enjoyed by this group of writers includes academe, the business world, government and the military. It is to their credit that they have given of their precious time and energy to become involved in the compilation of this book.

In previous revisions of this publication the monographs in Parts 6 and 7 had been designated as being of major or minor import and those judged of lesser note were relegated to the end of each pharmacological category and printed in a smaller type. However, with this edition every drug substance, diagnostic agent and pharmaceutical necessity is included as a full monograph, in regular alphabetic order, thus eliminating the requirement of searching in more than one location for similar type drugs. Every monograph has been checked for accuracy and timeliness. References to deleted monographs appear at the proper locations in the text.

Those familiar with the wonders of searching a data base using a CD-ROM will welcome this adjunct to the book and

little more need be said. If you are not acquainted with this fascinating method of information retrieval, a treat awaits. This new technology has not yet completely replaced the printed word and special pains have been taken (facilitated by the computer) to insure an adequate, though old-fashioned search facility—an index. Due to the proliferation of abbreviations and acronyms in the scientific literature, it became evident at an early stage that a glossary which defined the many acronyms employed throughout the text would be advantageous and was thus included.

Many constraints exist which dictate a maximum of about 2000 pages for this text. It was only through the combined efforts of the authors, Section Editors, the Editorial Board and the Mack Publishing Company that this target was achieved without loss of essential information. Many readers inquire as to why Lugol's Solution or Whitfield's Ointment is no longer discussed as they feel that *Remington*, to be complete, should retain all of the monographs included in the first edition as well as the new material generated over the past century! Certainly, this is an impossibility and it is hoped the user will have a modicum of compassion.

One section editor who has been associated with *Remington* for the past 35 years, Dr Grafton Chase, passed away during the latter stages of this revision period. Dr Chase developed the first chapters devoted to Radiopharmacy and was a pioneer in the science of radiochemistry. His participation will be missed.

Two new members of the Editorial Board, Drs Glen Hanson and H Steve White have adequately filled the void left by the retirement of Drs Ewart Swinyard and Stewart Harvey. They were up to the task of searching out new authors and revising the several chapters within their own expertise in Parts 5 and 6.

The Mack Publishing Company and their subsidiary, Science Press, have made the editorial responsibilities much more palatable. An editor could not have had a more responsive, compassionate and cooperative publisher. Through Mr Paul Mack and Ms Ruth Dalrymple at Mack and Ms Liz Bobier at Science Press, our liaison personnel, the task of producing this work was pleasurable.

Finally, Mr John Hoover, as Managing Editor for many, many revisions and Mrs Bonnie Packer, in her second term as Editorial Assistant, have provided the support which is unglamorous, little recognized, but without which no book can be assembled. They scrutinized every word, photograph, table, chart and drawing to ferret out typos and errors of commission and omission. Although we were not always of the same opinion regarding the numerous decisions required during the revision process, we still remain friends.

Philadelphia, January 1995

ARG

Table of Contents

Volume I

Part 1 Orientation

1 Scope	3
2 Evolution of Pharmacy	7
3 Ethics	18
4 Community Pharmacy	25
5 Pharmacists in Industry	29
6 Pharmacists in Government	33
7 Drug Information	42
8 Research	52

Part 2 Pharmaceutics

9 Metrology and Calculation	63
10 Statistics	94
11 Computer Science	128
12 Calculus	135
13 Molecular Structure, Properties and States of Matter	147
14 Complex Formation	169
15 Thermodynamics	184
16 Solutions and Phase Equilibria	194
17 Ionic Solutions and Electrolytic Equilibria	213
18 Reaction Kinetics	231
19 Interfacial Phenomena	241
20 Colloidal Dispersions	252
21 Coarse Dispersions	278
22 Rheology	292

Part 3 Pharmaceutical Chemistry

23 Inorganic Pharmaceutical Chemistry	315
24 Organic Pharmaceutical Chemistry	340
25 Fundamentals of Radioisotopes	364
26 Natural Products	382
27 Drug Nomenclature—United States Adopted Names	413
28 Structure-Activity Relationship and Drug Design	425

Part 4 Pharmaceutical Testing, Analysis and Control

29 Analysis of Medicinals	437
30 Biological Testing	491
31 Clinical Analysis	501
32 Chromatography	534
33 Instrumental Methods of Analysis	559
34 Dissolution	593
35 Bioavailability and Bioequivalency Testing	605
36 Tonicity, Osmoticity, Osmolality and Osmolarity	613
37 Separation	628
38 Stability of Pharmaceutical Products	639
39 Quality Assurance and Control	648

Part 5 Pharmacodynamics

40 Diseases: Manifestations and Pathophysiology	655
41 Drug Absorption, Action and Disposition	697
42 Basic Pharmacokinetics	724
43 Clinical Pharmacokinetics	741
44 Principles of Immunology	752
45 Adverse Drug Reactions	761
46 Pharmacogenetics	775
47 Pharmacological Aspects of Drug Abuse	780
48 Introduction of New Drugs	795
49 Biotechnology and Drugs	809
50 Alternative Healthcare	829

Volume II

Part 6 Pharmaceutical and Medicinal Agents

51 Medical Applications of Radioisotopes	843
52 Topical Drugs	866
53 Gastrointestinal and Liver Drugs	886
54 Blood, Fluids, Electrolytes and Hematologic Drugs	910
55 Cardiovascular Drugs	943
56 Respiratory Drugs	971
57 Sympathomimetic Drugs	981
58 Cholinomimetic Drugs	1000
59 Adrenergic and Adrenergic Neuron Blocking Drugs	1009
60 Antimuscarinic and Antispasmodic Drugs	1020
61 Skeletal Muscle Relaxants	1027
62 Diuretic Drugs	1039
63 Uterine and Antimigraine Drugs	1052
64 Hormones	1057
65 Vitamins and Other Nutrients	1106
66 Enzymes	1137
67 General Anesthetic Drugs	1140
68 Local Anesthetic Drugs	1146
69 Sedative and Hypnotic Drugs	1154
70 Antiepileptic Drugs	1171
71 Psychopharmacologic Agents	1180
72 Antipyretic and Anti-inflammatory Drugs	1196
73 Histamine and Antihistaminic Drugs	1222
74 Central Nervous System Stimulants	1231
75 Antineoplastic and Immunoactive Drugs	1236
76 Anti-infective Drugs	1263
77 Parasitocides	1337
78 Pesticides	1343
79 Diagnostic Agents	1365
80 Pharmaceutical Necessities	1380
81 Immunizing Agents and Diagnostic Skin Antigens	1417
82 Allergenic Extracts	1434

Part 7 Industrial Pharmacy

83 Preformulation	1447
84 Sterilization	1463
85 Plastic Packaging Materials	1487
86 Solutions, Emulsions, Suspensions and Extracts	1495
87 Parenteral Preparations	1524
88 Intravenous Admixtures	1549
89 Ophthalmic Preparations	1563
90 Medicated Applications	1577
91 Powders	1598
92 Oral Solid Dosage Forms	1615
93 Coating of Pharmaceutical Dosage Forms	1650
94 Sustained-Release Drug Delivery Systems	1660
95 Aerosols	1676

Part 8 Pharmacy Practice

96 Ambulatory Patient Care	1695
97 Institutional Patient Care	1720
98 Long-Term Care Facilities	1740
99 The Pharmacist and Public Health	1755
100 The Patient: Behavioral Determinants	1773
101 Patient Communication	1779
102 Drug Education	1786
103 Patient Compliance	1796
104 The Prescription	1808

105 Drug Interactions	1822
106 Clinical Drug Literature	1837
107 Health Accessories	1842
108 Surgical Supplies	1873
109 Poison Control	1883
110 Laws Governing Pharmacy	1892
111 Community Pharmacy Economics and Management ..	1913
112 Pharmacoeconomics	1929

Appendix

Dose Equivalents	A1
Periodic Chart	A2
Logarithms	A4

Glossary and Index

Alphabetic Index	I1
Glossary	G1

CHAPTER 36

Tonicity, Osmoticity, Osmolality and Osmolarity

Irwin Reich, BSc

Instructor and Manager, Pharmacy Laboratory

Roger Schnaare, PhD

Professor of Pharmacy

Edwin T Sugita, PhD

Professor and Chairman, Pharmaceutics Dept
Philadelphia College of Pharmacy and Science
Philadelphia, PA 19104

Basic Definitions

If a solution is placed in contact with a membrane that is permeable to molecules of the solvent, but not to molecules of the solute, the movement of solvent through the membrane is called osmosis. Such a membrane often is called *semipermeable*. As the several types of membranes of the body vary in their permeability, it is well to note that they are *selectively* permeable. Most normal living-cell membranes maintain various solute concentration gradients. A selectively permeable membrane may be defined either as one that does not permit free, unhampered diffusion of all the solutes present, or as one that maintains at least one solute concentration gradient across itself. Osmosis, then, is the diffusion of water through a membrane that maintains at least one solute concentration gradient across itself.

Assume Solution A is on one side of the membrane, and Solution B of the same solute but of a higher concentration is on the other side; the solvent will tend to pass into the more concentrated solution until equilibrium has been established. The pressure required to prevent this movement is the osmotic pressure. It is defined as the excess pressure, or pressure greater than that above the pure solvent, which must be applied to Solution B to prevent passage of solvent through a perfect semipermeable membrane from A to B. The concentration of a solution with respect to effect on osmotic pressure is related to the number of particles (unionized molecules, ions, macromolecules, aggregates) of solute(s) in solution and thus is affected by the degree of ionization or aggregation of the solute. See Chapter 16 for review of colligative properties of solutions.

Body fluids, including blood and lacrimal fluid, normally have an osmotic pressure which often is described as corresponding to that of a 0.9% solution of sodium chloride. The body also attempts to keep the osmotic pressure of the contents of the gastrointestinal tract at about this level, but there the normal range is much wider than that of most body fluids. The 0.9% sodium chloride solution is said to be *iso-osmotic* with physiological fluids. The term *isotonic*, meaning equal tone, is in medical usage commonly used interchangeably with isoosmotic. However, terms such as isotonic and tonicity should be used *only* with reference to a physiologic fluid. Isoosmotic actually is a physical term which compares the osmotic pressure (or another colligative property, such as freezing-point depression) of two liquids, neither of which may be a physiological fluid, or which may be a physiological fluid only under certain circumstances. For example, a solution of boric acid that is isoosmotic with both blood and lacrimal fluid is isotonic only with the lacrimal fluid. This solution causes hemolysis of red blood cells because molecules of boric acid pass freely through the erythrocyte membrane regardless of concentration. Thus, isotonicity infers a sense of physiological compatibility where isoosmoticity need

not. As another example, a "chemically defined elemental diet" or enteral nutritional fluid can be iso-osmotic with the contents of the gastrointestinal tract, but would not be considered a physiological fluid, or suitable for parenteral use.

A solution is isotonic with a living cell if there is no net gain or loss of water by the cell, or other change in the cell when it is in contact with that solution. Physiological solutions with an osmotic pressure lower than that of body fluids, or of 0.9% sodium chloride solution, are referred to commonly as being *hypotonic*. Physiological solutions having a greater osmotic pressure are termed *hypertonic*.

Such qualitative terms are of limited value, and it has become necessary to state osmotic properties in quantitative terms. To do so, a term must be used that will represent all the particles which may be present in a given system. The term used is *osmol*. An osmol is defined as the weight, in grams, of a solute, existing in a solution as molecules (and/or ions, macromolecules, aggregates, etc.), which is osmotically equivalent to a mole of an ideally behaving nonelectrolyte. Thus, the osmol-weight of a nonelectrolyte, in a dilute solution, generally is equal to its gram-molecular-weight. A milliosmol, abbreviated mOsm, is the weight stated in milligrams.

If one extrapolates this concept of relating an osmol and a mole of a nonelectrolyte as being equivalent, then one also may define an osmol in the following ways. It is the amount of solute which will provide one Avogadro's number (6.02×10^{23}) of particles in solution and it is the amount of solute which, on dissolution in 1 kg of water, will result in an osmotic pressure increase of 17,000 torr at 0° or 19,300 torr at 37°. One mOsmol is one-thousandth of an osmol. For example, 1 mole of anhydrous dextrose is equal to 180 g. One osmol of this nonelectrolyte is also 180 g. One mOsmol would be 180 mg. Thus 180 mg of this solute dissolved in 1 kg of water will produce an increase in osmotic pressure of 19.3 torr at body temperature.

For a solution of an electrolyte such as sodium chloride, one molecule of sodium chloride represents one sodium and one chloride ion. Hence, one mol will represent 2 osmols of sodium chloride theoretically. Accordingly, 1 osmol NaCl = 58.5 g/2 or 29.25 g. This quantity represents the sum total of 6.02×10^{23} ions as the total number of particles. Ideal solutions infer very dilute solutions or infinite dilution. However, as the concentration is increased, other factors enter. With strong electrolytes, interionic attraction causes a decrease in their effect on colligative properties. In addition, and in opposition, for all solutes, including nonelectrolytes, solvation and possibly other factors operate to intensify their colligative effect. Therefore, it is very difficult and often impossible to predict accurately the osmoticity of a solution. It may be possible to do so for a dilute solution of a single, pure and well-characterized solute, but not for most parenteral and enteral medicinal and/or nutritional fluids; experimental determination likely is required.

Therapeutic Considerations

It generally is accepted that osmotic effects have a major place in the maintenance of homeostasis (the state of equilibrium in the living body with respect to various functions and to the chemical composition of the fluids and tissues, eg, temperature, heart rate, blood pressure, water content or blood sugar). To a great extent these effects occur within or between cells and tissues where they cannot be measured. One of the most troublesome problems in clinical medicine is the maintenance of adequate body fluids and proper balance between extracellular and intracellular fluid volumes in seriously ill patients. It should be kept in mind, however, that fluid and electrolyte abnormalities are not diseases, but are the manifestations of disease.

The physiological mechanisms which control water intake and output appear to respond primarily to serum osmoticity. Renal regulation of output is influenced by variation in rate of release of pituitary antidiuretic hormone (ADH) and other factors in response to changes in serum osmoticity. Osmotic changes also serve as a stimulus to moderate thirst. This mechanism is sufficiently sensitive to limit variations in osmoticity in the normal individual to less than about 1%. Body fluid continually oscillates within this narrow range. An increase of plasma osmoticity of 1% will stimulate ADH release, result in reduction of urine flow and, at the same time, stimulate thirst that results in increased water intake. Both the increased renal reabsorption of water (without solute) stimulated by circulating ADH and the increased water intake tend to lower serum osmoticity.

The transfer of water through the cell membrane occurs so rapidly that any lack of osmotic equilibrium between the two fluid compartments in any given tissue usually is corrected within a few seconds and, at most, within a minute or so. However, this rapid transfer of water does not mean that complete equilibration occurs between the extracellular and intracellular compartments throughout the entire body within this same short period of time. The reason is that fluid usually enters the body through the gut and then must be transported by the circulatory system to all tissues before complete equilibration can occur. In the normal person it may require 30 to 60 min to achieve reasonably good equilibration throughout the body after drinking water. Osmoticity is the property that largely determines the physiologic acceptability of a variety of solutions used for therapeutic and nutritional purposes.

Pharmaceutical and therapeutic consideration of osmotic effects has been, to a great extent, directed toward the side effects of ophthalmic and parenteral medicinals due to abnormal osmoticity, and to either formulating to avoid the side effects or finding methods of administration to minimize them. More recently this consideration has been extended to total (central) parenteral nutrition, to enteral hyperalimentation ("tube" feeding) and to concentrated-fluid infant formulas.¹ Also, in recent years, the importance of osmometry of serum and urine in the diagnosis of many pathological conditions has been recognized.

There are a number of examples of the direct therapeutic effect of osmotic action, such as the intravenous use of mannitol as a diuretic which is filtered at the glomeruli and thus increases the osmotic pressure of tubular urine. Water must then be reabsorbed against a higher osmotic gradient than otherwise, so reabsorption is slower and diuresis is observed. The same fundamental principle applies to the intravenous administration of 30% urea used to affect intracranial pressure in the control of cerebral edema. Peritoneal dialysis fluids tend to be somewhat hyperosmotic to withdraw water and nitrogenous metabolites. Two to five percent sodium chloride solutions or dispersions in an oleaginous base (Muro, *Bausch & Lomb*) and a 40% glucose ointment are used topically for corneal edema. Ophthalmic (Wyeth-Ayerst) is ophthalmic glycerin employed for its osmotic effect to clear edematous cornea to facilitate an ophthalmoscopic or gonioscopic examination. Glycerin solutions in 50% concentration [Osmoglyn (*Alcon*)] and isosorbide solution [Ismotec (*Alcon*)]

are oral osmotic agents for reducing intraocular pressure. The osmotic principle also applies to plasma extenders such as polyvinylpyrrolidone and to saline laxatives such as magnesium sulfate, magnesium citrate solution, magnesium hydroxide (via gastric neutralization), sodium sulfate, sodium phosphate and sodium biphosphate oral solution and enema (*Fleet*).

An interesting osmotic laxative which is a nonelectrolyte is a lactulose solution. Lactulose is a nonabsorbable disaccharide which is colon-specific, wherein colonic bacteria degrade some of the disaccharide to lactic and other simple organic acids. These, *in toto*, lead to an osmotic effect and laxation. An extension of this therapy is illustrated by Cephulac (*Marion Merrell Dow*) solution, which uses the acidification of the colon via lactulose degradation to serve as a trap for ammonia migrating from the blood to the colon. The conversion of ammonia of blood to the ammonium ion in the colon ultimately is coupled with the osmotic effect and laxation, thus expelling undesirable levels of blood ammonia. This product is employed to prevent and treat frontal systemic encephalopathy.

Osmotic laxation is observed with the oral or rectal use of glycerin and sorbitol. Epsom salt has been used in baths and compresses to reduce edema associated with sprains. Another approach is the indirect application of the osmotic effect in therapy via osmotic pump drug delivery systems.²

Osmolality and Osmolarity

It is necessary to use several additional terms to define expressions of concentration in reflecting the osmoticity of solutions. The terms include osmolality, the expression of osmolal concentration and osmolarity, the expression of osmolar concentration.

Osmolality—A solution has an osmolal concentration of one when it contains 1 osmol of solute/kg of water. A solution has an osmolality of n when it contains n osmoles/kg of water. Osmolal solutions, like their counterpart molal solutions, reflect a weight-to-weight relationship between the solute and the solvent. Since an osmol of any nonelectrolyte is equivalent to 1 mol of that compound, then a 1 osmolal solution is synonymous to a 1 molal solution for a typical nonelectrolyte.

With a typical electrolyte like sodium chloride, 1 osmol is approximately 0.5 mol of sodium chloride. Thus, it follows that a 1 osmolal solution of sodium chloride essentially is equivalent to a 0.5 molal solution. Recall that a 1 osmolal solution of dextrose or sodium chloride each will contain the same particle concentration. In the dextrose solution there will be 6.02×10^{23} molecules/kg of water and in the sodium chloride solution one will have 6.02×10^{23} total ions/kg of water, one-half of which are Na^+ ions and the other half Cl^- ions.

As in molal solutions, osmolal solutions usually are employed where quantitative precision is required, as in the measurement of physical and chemical properties of solutions (ie, colligative properties). The advantage of the w/w relationship is that the concentration of the system is not influenced by temperature.

Osmolarity—The relationship observed between molality and osmolality is shared similarly between molarity and osmolarity. A solution has an osmolar concentration of 1 when it contains 1 osmol of solute/L of solution. Likewise, a solution has an osmolarity of n when it contains n osmoles/L of solution. Osmolar solutions, unlike osmolal solution, reflect a weight in volume relationship between the solute and final solution. A 1 molar and 1 osmolar solution would be identical for nonelectrolytes. For sodium chloride a 1 osmolar solution would contain 1 osmol of sodium chloride per liter which approximates a 0.5 molar solution. The advantage of employing osmolar concentrations over osmolal concentrations is the ability to relate a specific number of osmoles or milliosmoles to a volume, such as a liter or mL. Thus, the osmolar concept is simpler and more practical. Volumes of

solution, rather than weights of solution, are more practical in the delivery of liquid dosage forms.

Many health professionals do not have a clear understanding of the difference between osmolality and osmolality. In fact, the terms have been used interchangeably. A 1 osmolar solution of a solute always will be more concentrated than a 1 osmolal solution. With dilute solutions the difference may be acceptably small. For example, a 0.9% *w/v* solution of sodium chloride in water contains 9 g of sodium chloride/L of solution, equivalent to 0.308 osmolar; or 9 g of sodium chloride/996.5 g of water, equivalent to 0.309 osmolal, less than a 1% error. For concentrated solutions the % difference between osmolality and osmolality is much greater and may be highly significant; 3.5% for 5% *w/v* dextrose solution and 25% for 25% *w/v* dextrose solution. One should be alerted to the sizable errors which may occur with concentrated solutions or fluids, such as those employed in total parenteral nutrition, enteral hyperalimentation and oral nutritional fluids for infants.

Reference has been made to the terms hypertonic and hypotonic. Analogous terms are hyperosmotic and hypoosmotic. Assuming normal serum osmolality to be 285 mOsmol/kg, as serum osmolality increases due to water deficit, the following signs and symptoms usually are found to accumulate progressively at approximately these values: 294 to 298—thirst (if the patient is alert and communicative); 299 to 313—dry mucous membranes; 314 to 329—weakness, doughy skin; above 330—disorientation, postural hypotension, severe weakness, fainting, CNS changes, stupor and coma. As serum osmolality decreases due to water excess the following may occur: 275 to 261—headache; 262 to 251—drowsiness, weakness; 250 to 233—disorientation, cramps; below 233—seizures, stupor and coma.

As indicated previously, the mechanisms of the body actively combat such major changes by limiting the variation in osmolality for normal individuals to less than about 1% (approximately in the range 282 to 288 mOsmol/kg, based on the above assumption).

The value given for normal serum osmolality above was described as an assumption because of the variety of values found in the literature. Serum osmolality often is stated loosely to be about 300 mOsmol/L. Various references report 280 to 295 mOsmol/L; 275 to 300 mOsmol/L; 290 mOsmol/L; 306 mOsmol/L and 275 to 295 mOsmol/kg.

Reference has been made to confusion in the use of the terms osmolality and osmolality, a distinction of special importance for nutritional fluids. Awareness of high concentrations of infant-formula should give warning as to possible risks. Unfortunately, the osmoticity of infant formulas, tube feedings and total parenteral nutrition solutions has not been described adequately either in textbooks or in the literature,³ and the labels of many commercial nutritional fluids do not, in any way, state their osmoticity. Only recently have enteral fluids been characterized in terms of osmoticity. Some product lines now are accenting isoosmotic enteral nutritional supplements. Often, when the term osmolality is used, one cannot discern whether this simply is incorrect terminology, or if osmolality actually has been calculated from osmolality.

Another current practice which can cause confusion, is the use of the terms *normal* and/or *physiological* for isotonic sodium chloride solution (0.9%). The solution surely is isoosmotic. However, as to being physiological, the concentration of ions are each of 154 mEq/L while serum contains about 140 mEq of sodium and about 103 mEq of chloride.

The range of mOsmol values found for serum raises the question as to what really is meant by the terms hypotonic and hypertonic for medicinal and nutritional fluids. One can find the statement that fluids with an osmolality of 50 mOsmol or more above normal are hypertonic and, if 50 mOsmol or more below normal, are hypotonic. One also can find the statement that peripheral infusions should not have an osmolality exceeding 700 to 800 mOsmol/L.⁴ Examples of osmol concentrations of solutions used in peripheral infusions are: (D5W) 5% dextrose solution—252 mOsmol/L; (D10W) 10% dextrose solution—505 mOsmol/L; Lactated Ringer's 5% Dex-

trose—525 mOsmol/L. When a fluid is hypertonic, undesirable effects often can be decreased by using relatively slow rates of infusion, and/or relatively short periods of infusion. 25% dextrose solution (D25W)—4.25% Amino Acids is a representative example of a highly osmotic hyperalimentation solution. It has been stated that when osmolal loading is needed, a maximum safe tolerance for a normally hydrated subject would be an approximate increase of 25 mOsmol/kg of water over 4 hours.³

Computation of Osmolality

Several methods are used to obtain numerical values of osmolality. The osmolal concentration, sometimes referred to as the "theoretical osmolality," is calculated from the *w/v* concentration using the following equation:

$$\frac{\text{g}}{\text{L}} \times \frac{\text{mols}}{\text{g}} \times \frac{\text{osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} = \frac{\text{mOsmol}}{\text{L}} \quad (1)$$

The number of osmols/mol is equal to 1 for nonelectrolytes and is equal to the number of ions per molecule for strong electrolytes.

This calculation, omits consideration of factors such as solvation and interionic forces. By this method of calculation 0.9% sodium chloride has an osmolal concentration of 308 mOsmol/L and a concentration of 154 mOsmol/L in either sodium or chloride ion.

Two other methods compute osmolality from values of osmolality. The determination of osmolality will be discussed later. One method has a strong theoretical basis of physical-chemical principles⁵ using values of the partial molal volume(s) of the solute(s). A 0.9% sodium chloride solution, found experimentally to have an osmolality of 286 mOsmol/kg, was calculated to have an osmolality of 280 mOsmol/L, rather different from the value of 308 mOsmol/L calculated as above. The method, using partial molal volumes, is relatively rigorous, but many systems appear to be too complex and/or too poorly defined to be dealt with by this method.

The other method is based on calculating the weight of water from the solution density and concentration

$$\frac{\text{g water}}{\text{mL solution}} = \frac{\text{g solution}}{\text{mL solution}} - \frac{\text{g solute}}{\text{mL solution}}$$

then

$$\begin{aligned} \text{osmolality} \left(\frac{\text{mOsmol}}{\text{L solution}} \right) \\ = \text{osmolality} \left(\frac{\text{mOsmol}}{1000 \text{ g water}} \right) \times \frac{\text{g water}}{\text{mL solution}} \end{aligned}$$

The experimental value for the osmolality of 0.9% sodium chloride solution was 292.7 mOsmol/kg; the value computed for osmolality was 291.4 mOsmol/L. This method uses easily obtained values of density of the solution and of its solute content and can be used with all systems. For example, the osmolality of a nutritional product was determined by the freezing-point depression method to be 625 mOsmol/kg;⁷ its osmolality was calculated as $625 \times 0.839 = 524 \text{ mOsmol/L}$.

Monographs in the USP for solutions which provide intravenous replenishment of fluid, nutrient(s) or electrolyte(s), and for osmotic diuretics such as Mannitol Injection, require the osmolal concentration be stated on the label in osmols/L, except that where the contents are less than 100 mL, or where the label states the article is not for direct injection but is to be diluted before use, the label alternatively may state the total osmolal concentration in mOsmol/mL.

An example of the use of the first method described above is the computation of the approximate osmolal concentration ("theoretical osmolality") of a Lactated Ringer's 5% Dextrose Solution (Abbott), which is labeled to contain, per L, dextrose (hydrous) 50 g, sodium chloride 6 g, potassium chloride 300 mg, calcium chloride 200 mg and sodium lactate

3.1 g. Also stated is that the total osmolar concentration of the solution is approximately 524 mOsmol per L, in part contributed by 130 mEq of Na^+ , 109 mEq of Cl^- , 4 mEq of K^+ , 3 mEq of Ca^{2+} and 28 mEq of lactate ion.

The derivation of the osmolar concentrations from the stated composition of the solution may be verified by calculations using Eq 1.

Dextrose

$$\frac{50 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{198 \text{ g}} \times \frac{1 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{Osmol}} = 252 \text{ mOsmol/L}$$

Sodium Chloride

$$\frac{6 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{58.4 \text{ g}} \times \frac{2 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} = 205 \frac{\text{mOsmol}}{\text{L}} \left\{ \begin{array}{l} (102.7 \text{ mOsmol Na}^+) \\ (102.7 \text{ mOsmol Cl}^-) \end{array} \right.$$

Potassium Chloride

$$\frac{0.3 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{74.6 \text{ g}} \times \frac{2 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} = \frac{8.04 \text{ mOsmol}}{\text{L}} \left\{ \begin{array}{l} (4.02 \text{ mOsmol K}^+) \\ (4.02 \text{ mOsmol Cl}^-) \end{array} \right.$$

Calcium Chloride

$$\frac{0.2 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{111 \text{ g}} \times \frac{3 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} = \frac{5.41 \text{ mOsmol}}{\text{L}} \left\{ \begin{array}{l} (1.80 \text{ mOsmol Ca}^{2+}) \\ (3.61 \text{ mOsmol Cl}^-) \end{array} \right.$$

Sodium Lactate

$$\frac{3.1 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{112 \text{ g}} \times \frac{2 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} = \frac{55.4 \text{ mOsmol}}{\text{L}} \left\{ \begin{array}{l} (27.7 \text{ mOsmol Na}^+) \\ (27.7 \text{ mOsmol lactate}) \end{array} \right.$$

The total osmolar concentration of the five solutes in the solution is 526, in good agreement with the labeled total osmolar concentration of approximately 524 mOsmol/L.

The mOsmol of sodium in 1 L of the solution is the sum of the mOsmol of the ion from sodium chloride and sodium lactate, ie, $102 + 27.6 = 129.6$ mOsmol. Chloride ions come from the sodium chloride, potassium chloride and calcium chloride, the total osmolar concentration being $102 + 4.02 + 3.61 = 109.6$ mOsmol. The mOsmol values of potassium, calcium and lactate are calculated to be 4.02, 1.80 and 27.6, respectively.

The osmolality of a mixture of complex composition, such as an enteral hyperalimentation fluid, cannot be calculated with any acceptable degree of certainty and, therefore, the *osmolality* of such preparations should be determined experimentally.

Undesirable Effects of Abnormal Osmoticity

Ophthalmic Medication—It is generally accepted that ophthalmic preparations intended for instillation into the cul-de-sac of the eye should, if possible, be approximately isotonic to avoid irritation (see Chapter 89). It also has been stated that the abnormal tonicity of contact lens solutions can cause the lens to adhere to the eye and/or cause burning or dryness and photophobia.

Parenteral Medication—Osmoticity is of great importance in parenteral injections, its effects depending on the degree of deviation from tonicity, the concentration, the location of the injection, the volume injected, the speed of the injection, the rapidity of dilution and diffusion, etc. When formulating parenterals, solutions otherwise hypotonic usually have their tonicity adjusted by the addition of dextrose or sodium chloride. Hypertonic parenteral drug solutions cannot be adjusted. Hypotonic and hypertonic solutions usually are administered slowly in small volumes, or into a large vein such as the subclavian, where dilution and distribution occur rapidly. Solutions that differ from the serum in tonicity gen-

erally are stated to cause tissue irritation, pain on injection and electrolyte shifts, the effect depending on the degree of deviation from tonicity.

Excessive infusion of *hypotonic* fluids may cause swelling of red blood cells, hemolysis and water invasion of the body's cells in general. When this is beyond the body's tolerance for water, water intoxication results, with convulsions and edema, such as pulmonary edema.

Excessive infusion of *isotonic* fluids can cause an increase in extracellular fluid volume, which can result in circulatory overload.

Excessive infusion of *hypertonic* fluids leads to a wide variety of complications. For example, the sequence of events when the body is presented with a large intravenous load of hypertonic fluid, rich in dextrose, is as follows: hyperglycemia, glycosuria and intracellular dehydration, osmotic diuresis, loss of water and electrolytes, dehydration and coma.

One cause of osmotic diuresis is the infusion of dextrose at a rate faster than the ability of the patient to metabolize it (as greater than perhaps 400 to 500 mg/kg/hr for an adult on total parenteral nutrition). A heavy load of unmetabolizable dextrose increases the osmoticity of blood and acts as a diuretic; the increased solute load requires more fluid for excretion, 10 to 20 mL of water being required to excrete each gram of dextrose. Solutions, such as those for total parenteral nutrition, should be administered by means of a metered constant-infusion apparatus over a lengthy period (usually more than 24 hours) to avoid sudden hyperosmotic dextrose loads. Such solutions may cause osmotic diuresis; if this occurs, water balance is likely to become negative because of the increased urinary volume, and electrolyte depletion may occur because of excretion of sodium and potassium secondary to the osmotic diuresis. If such diuresis is marked, body weight falls abruptly and signs of dehydration appear. Urine should be monitored for signs of osmotic diuresis, such as glycosuria and increased urine volume.

If the intravenous injection rate of hypertonic solution is too rapid, there may be catastrophic effects on the circulatory and respiratory systems. Blood pressure may fall to dangerous levels, cardiac irregularities or arrest may ensue, respiration may become shallow and irregular and there may be heart failure and pulmonary edema. Probably the precipitating factor is a bolus of concentrated solute suddenly reaching the myocardium and the chemoreceptors in the aortic arch and carotid sinus.³

Abrupt changes in serum osmoticity can lead to cerebral hemorrhage. It has been shown experimentally that rapid infusions of therapeutic doses of hypertonic saline with osmotic loads produce a sudden rise in cerebrospinal fluid (CSF) pressure and venous pressure (VP) followed by a precipitous fall in CSF pressure. This particularly may be conducive to intracranial hemorrhage, as the rapid infusion produces an increase in plasma volume and venous pressure at the same time the CSF pressure is falling. During the CSF pressure rise, there is a drop in hemoglobin and hematocrit, reflecting a marked increase in blood volume.

Hyperosmotic medications, such as sodium bicarbonate (osmolality of 1560 at 1 mEq/mL), which are administered intravenously, should be diluted prior to use and should be injected slowly to allow dilution by the circulating blood. Rapid "push" injections may cause a significant increase in blood osmoticity.⁵

As to other possibilities, there may be crenation of red blood cells and general cellular dehydration. Hypertonic dextrose or saline, etc, infused through a peripheral vein with small blood volume may traumatize the vein and cause thrombophlebitis. Infiltration can cause trauma and necrosis of tissues. Safety, therefore, demands that all intravenous injections, especially highly osmotic solutions, be performed slowly, usually being given preferably over a period not less than that required for a complete circulation of the blood, eg, 1 minute. The exact danger point varies with the

state of the patient, the concentration of the solution, the nature of the solute and the rate of administration.

Hyperosmotic solutions also should not be discontinued suddenly. In dogs, marked increase in levels of intracranial pressure occur when hyperglycemia produced by dextrose infusions is reversed suddenly by stopping the infusion and administering saline. It also has been shown that the CSF pressure in humans rises during treatment of diabetic ketoacidosis in association with a fall in the plasma concentration of dextrose and a fall in plasma osmolality. These observations may be explained by the different rates of decline in dextrose content of the brain and of plasma. The concentration of dextrose in the brain may fall more slowly than in the plasma, causing a shift of fluid from the extracellular fluid space to the intracellular compartment of the CNS, resulting in increased intracranial pressure.

Osmometry and the Clinical Laboratory

Serum and urine osmometry may assist in the diagnosis of certain fluid and electrolyte problems. However, osmometry values have little meaning unless the clinical situation is known. Osmometry is used in renal dialysis as a check on the electrolyte composition of the fluid. In the clinical laboratory, as stated above, the term "osmolality" is used generally, but usually is reported as mOsmol/L. It may seem unnecessary to mention that osmolality depends not only on the number of solute particles, but also on the quantity of water in which they are dissolved. However, it may help one to understand the statement that the normal range of urine osmolality is 50 to 1400 mOsmol/L, and for a random specimen is 500 to 800 mOsmol/L.

Serum Osmoticity

Sodium is by far the principal solute involved in serum osmoticity. Therefore, abnormal serum osmoticity is most likely to be associated with conditions that cause abnormal sodium concentration and/or abnormal water volume.

Thus, hyperosmotic serum is likely to be caused by an increase in serum sodium and/or loss of water. It may be associated with diabetes insipidus, hypercalcemia, diuresis during severe hyperglycemia or with early recovery from renal shutdown. Alcohol ingestion is said to be the most common cause of the hyperosmotic state and of coexisting coma and the hyperosmotic state. An example of hyperosmoticity is a comatose diabetic with a serum osmoticity of 365 mOsmol/L.

In a somewhat analogous fashion, hypoosmotic serum is likely to be due to decrease in serum sodium and/or excess of water. It may be associated with the postoperative state (especially with excessive water replacement therapy), treatment with diuretic drugs and low-salt diet (as with patients with heart failure, cirrhosis, etc), adrenal disease (eg, Addison's disease, adrenogenital syndrome) or SIADH (syndrome of inappropriate ADH secretion). There are many diseases which cause ADH to be released inappropriately (ie, in spite of the fact that serum osmoticity and volume may have been normal initially). These include oat-cell carcinoma of the lung, bronchogenic carcinoma, congestive heart failure, inflammatory pulmonary lesions, porphyria, severe hypothyroidism or cerebral disease (such as tumor, trauma, infection, vascular abnormalities, etc). It also may be found with some patients with excessive diuretic use. Serum and urine osmoticity are measured when SIADH is suspected. In SIADH there is hypoosmoticity of the blood in association with a relative hyperosmoticity of urine. The usual cause is a malfunction of the normal osmotic response of osmoreceptors, an excess of exogenous vasopressin, or a production of a vasopressin-like hormone that is not under the regular control of serum osmoticity. The diagnosis is made by simultaneous measurement of urine and serum osmolality. The serum osmolality will be lower than normal and much lower than the urine osmolality, indicating inappropriate secretion of a concentrated urine in the presence of a dilute serum.

Cardiac, renal and hepatic disease characteristically reduce the sodium/osmolality ratio, this being partially attributed to the effects of increased blood sugar, urea or unknown metabolic products. Patients in shock may develop disproportionately elevated measured osmolality compared to calculated osmolality, which points toward the presence of circulating metabolic products.

There are several approximate methods for estimating serum osmolality from clinical laboratory values for sodium ion, etc. They may be of considerable value in an emergency situation.

1. Serum osmolality may be estimated from

$$\text{mOsmol} = (1.86 \times \text{sodium}) + \frac{\text{blood sugar}}{18} + \frac{\text{BUN}}{2.8} + 5$$

(Na in mEq/L, blood sugar and BUN in mg/100 mL)

2. A quick approximation is

$$\text{mOsmol} = 2 \text{ Na} + \frac{\text{BS}}{20} + \frac{\text{BUN}}{3}$$

3. The osmolality is usually, *but not always*, very close to two times the sodium reading plus 10.

Urine Osmoticity

The two main functions of the kidney are glomerular filtration and tubular reabsorption. Clinically, tubular function is measured best by tests that determine the ability of the tubules to concentrate and dilute the urine. Tests of urinary dilution are not as sensitive in the detection of disease, as are tests of urinary concentration. As concentration of urine occurs in the renal medulla (interstitial fluids, loops of Henle, capillaries of the medulla and collecting tubules), the disease processes that disturb the function or structure of the medulla produce early impairment of the concentrating power of the kidney. Such diseases include acute tubular necrosis, obstructive uropathy, pyelonephritis, papillary necrosis, medullary cysts, hypokalemic and hypercalcemic nephropathy and sickle-cell disease.

Measurement of urine osmolality is an accurate test for the diluting and concentrating ability of the kidneys. In the absence of ADH, the daily urinary output is likely to be 6 to 8 L, or more. The normal urine osmolality depends on the clinical setting; normally, with maximum ADH stimulation, it can be as much as 1200 mOsmol/kg, and with maximum ADH suppression as little as 50 mOsmol/kg. Simultaneous determination of serum and urine osmolality often is valuable in assessing the distal tubular response to circulating ADH. For example, if the patient's serum is hyperosmotic, or in the upper limits of normal ranges, and the patient's urine osmolality measured at the same time is much lower, a decreased responsiveness of the distal tubules to circulating ADH is suggested.

Measurement of urine osmolality during water restriction is an accurate, sensitive test of decreased renal function. For example, under the conditions of one test, normal osmolality would be greater than 800 mOsmol/kg. With severe impairment the value would be less than 400 mOsmol/kg. Knowledge of urine osmolality may point to a problem even though other tests are normal (eg, the Fishberg concentration test, BUN, PSP excretion, creatinine clearance or IV pyelogram). Knowledge of its value may be useful especially in diabetes mellitus, essential hypertension and silent pyelonephritis. The urine/serum osmolality ratio should be calculated and should be equal to or greater than 3.

Osmoticity and Enteral Hyperalimentation

Some aspects of nutrition are discussed briefly here because of the potential major side effects due to abnormal osmoticity of nutritional fluids, and because there exists in-

creasing dialogue on nutrition among pharmacists, dietitians, nurses and physicians. An example is the professional organization, ASPEN (The American Society for Parenteral and Enteral Nutrition), with membership open to all of the above health practitioners. It is desirable, therefore, that pharmacists be able to discuss these matters with these other health professionals in terms of nutrition as well as medicine.

Osmoticity has been of special importance in the intravenous infusion of large volumes of highly concentrated nutritional solutions. Their hyperosmoticity has been a major factor in the requirement that they be injected centrally into a large volume of rapidly moving blood, instead of using peripheral infusion. Use of such solutions and knowledge of their value have led, more recently, to the use of similar formulations administered, not parenterally, but by instillation into some part of the gastrointestinal tract, orally, by nasogastric tube, feeding gastrostomy or by needle-catheter jejunostomy. This method has given excellent total nutrition, for a period of time, to many patients and obviously avoids some of the problems associated with injections.

Enteral nutritional formulas can be modular allowing individual supplementation of protein, carbohydrate or fat. Other formulas are called "defined formula diets" and contain protein, carbohydrate, fat, minerals and vitamins. These nutritionally complete formulations can be monomeric (or oligomeric), based on amino acids, short peptides and simple carbohydrates or polymeric, based on complex protein and carbohydrates.

These diets are necessarily relatively high in osmoticity because their smaller molecules result in more particles per gram than in normal foods. An example is a fluid consisting of: L-amino acids, dextrose oligosaccharides, vitamins (including fat-soluble vitamins), fat as a highly purified safflower oil or soybean oil, electrolytes, trace minerals and water. As it contains fat, that component is not in solution and therefore should have no direct effect on osmoticity. However, the potential for interactions can cause some significant changes in total particle concentration and indirectly affect the osmoticity.⁸

Although easily digested, dextrose contributes more particles than most other carbohydrate sources, such as starch, and is more likely to cause osmotic diarrhea, especially with bolus feeding. Osmoticity is improved (decreased) by replacing dextrose with dextrose oligosaccharides (carbohydrates that yield on hydrolysis 2 to 10 monosaccharides). Flavoring also increases the osmoticity of a product, different flavors causing varying increases.

Commercial diets are packaged as fluids or as powders for reconstitution. Reconstitution is usually with water. These products are categorized on caloric density, (calories/mL), protein content or osmolality (mOsm/kg of H₂O). Parenteral nutritional products, on the other hand, are labeled in terms of osmolality (mOsm/L).

The enteric route for hyperalimentation frequently is overlooked in many diseases or post-trauma states, if the patient is not readily responsive to traditional oral feedings. Poor appetite, chronic nausea, general apathy and a degree of somnolence or sedation are common concomitants of serious disease. This frequently prevents adequate oral alimentation and results in progressive energy and nutrient deficits. Often, supplementary feedings of a highly nutritious formula are taken poorly or refused entirely. However, the digestive and absorptive capabilities of the gastrointestinal tract are frequently intact and, when challenged with appropriate nutrient fluids, can be used effectively. By using an intact GI tract for proper alimentation, the major problems of sepsis and metabolic derangement which relate to intravenous hyperalimentation largely are obviated, and adequate nutritional support is simplified greatly. Because of this increased safety and ease of administration, the enteric route for hyperalimentation should be used whenever possible.⁹

When ingested in large amounts or concentrated fluids, the osmotic characteristics of certain foods can cause an upset in the normal water balance within the body. For a given weight

of solute the osmolality of the solution is inversely proportional to the size of the particles. Nutritional components can be listed in an approximate order of decreasing osmotic effect per gram, as¹⁰

1. Electrolytes such as sodium chloride
2. Relatively small organic molecules such as dextrose (glucose) and amino acids
3. Dextrose oligosaccharides
4. Starches
5. Proteins
6. Fats (as fats are not water-soluble they have no osmotic effect)

Thus, in foods, high proportions of electrolytes, amino acids and simple sugars have the greatest effect on osmolality, and as a result, on tolerance. The approximate osmolality of a few common foods and beverages is

	mOsmol/kg
Whole milk	295
Tomato juice	595
Orange juice	935
Ice cream	1150

When nutrition of high osmoticity is ingested, large amounts of water will transfer to the stomach and intestines from the fluid surrounding those organs in an attempt to lower the osmoticity. The higher the osmoticity, the larger the amount of water required; a large amount of water in the GI tract can cause distention, cramps, nausea, vomiting, hypermotility and shock. The food may move through the tract too rapidly for the water to be reabsorbed, and result in diarrhea; severe diarrhea can cause dehydration. The hyperosmotic enteral effects have been observed by the administration of undiluted hypertonic oral medication;¹¹ Table I from this work lists average osmolality values of some commercially available drug solutions and suspensions. Thus, there is some analogy to the effect of hyperosmotic intravenous infusions.

Hyperosmotic feedings may result in mucosal damage in the GI tract. Rats given hyperosmotic feeding showed transient decrease in disaccharidase activity, and an increase in alkaline phosphatase activity. They also showed morphologic alterations in the microvilli of the small intestines. After a period of severe gastroenteritis, the bowel may be unusually susceptible to highly osmotic formulas, and their use may increase the frequency of diarrhea. Infant formulas that are hyperosmotic may affect preterm infants adversely during the early neonatal period, and they may produce or predispose neonates to necrotizing enterocolitis when delivered to the jejunum through a nasogastric tube.

The body attempts to keep the osmoticity of the contents of the stomach and intestines at approximately the same level as that of the fluid surrounding them. As a fluid of lower osmoticity requires the transfer of less water to dilute it, it should be tolerated better than one of higher osmoticity. As to tolerance, there is a great variation from one individual to another in sensitivity to the osmoticity of foods. The majority of patients receiving nutritional formulas, either orally or by tube, are able to tolerate feedings with a wide range of osmoticities if administered slowly and if adequate additional fluids are given. However, certain patients are more likely to develop symptoms of intolerance when receiving fluids of high osmoticity. These include debilitated patients, patients with GI disorders, pre- and postoperative patients, gastrostomy- and jejunostomy-fed patients and patients whose GI tracts have not been challenged for an extended period of time. Thus, osmoticity always should be considered in the selection of the formula for each individual patient. With all products, additional fluid intake may be indicated for individuals with certain clinical conditions. Frequent feedings of small volume or a continual instillation (pumped) may be of benefit initially in establishing tolerance to a formula. For other than isoosmotic formulas, feedings of reduced concentration (osmolality less than 400 mOsmol/kg) also may be helpful initially if tolerance problems arise in sensitive individuals. Concentration and size of feeding then can be increased gradually to normal as tolerance is established.

A common disturbance of intake encountered in elderly individuals relates to excess solid intake rather than to reduced water intake. For example, an elderly victim of a cerebral vascular accident who is being fed by nasogastric tube may be given a formula whose solute load requires a greatly increased water intake. Thus, tube feeding containing 120 g of protein and 10 g of salt will result in the excretion of more than 1000 mOsmol of solute. This requires the obligatory excretion of a volume of urine between 1200 and 1500 mL when the kidneys are capable of normal concentration ability. As elderly individuals often have significant impairment in renal function, water loss as urine may exceed 2000 to 2500 mL per day. Such an individual would require 3 to 4 L of water/day simply to meet the increased demand created by this high solute intake. Failure of the physician to provide such a patient with the increased water intake needed will result in a progressive water deficit which rapidly may become critical. The importance of knowing the complete composition of the tube feeding formulas used for incapacitated patients cannot be overemphasized.

Osmolality Determination

The need for experimental determination of osmolality has been established. In regard to this there are four properties of solutions that depend only on the number of "particles" in the solution. They are osmotic pressure elevation, boiling point elevation, vapor pressure depression and freezing point depression. These are called colligative properties and if one of them is known, the others can be calculated from its value. Osmotic pressure elevation is the most difficult to measure satisfactorily. The boiling-point elevation may be determined but the values are rather sensitive to changes in barometric pressure. Also, for an aqueous solution the molal boiling-point elevation is considerably less than the freezing-point depression. Thus, it is less accurate than the freezing-point method. Determinations of vapor-pressure lowering are quite easy, rapid and convenient. A vapor-pressure osmometer with a precision of <2 mOsmol/kg is reported by Dickerson, *et al.*¹¹ Another commonly used method is that of freezing-point depression, which can be determined quite readily with a fair degree of accuracy (see *Freezing-Point Depression*, Chapter 16). It should be noted that the data in Appendix A can be converted readily to vapor pressure lowering if desired.

The results of investigations by Lund *et al.*¹² indicate that the freezing point of normal, healthy human blood is -0.52° . Inasmuch as water is the medium in which the various constituents of blood are either suspended or dissolved in this method, it is assumed that any aqueous solution freezing at -0.52° is isotonic with blood. Now it is rare that a simple aqueous solution of the therapeutic agent to be injected parenterally has a freezing point of -0.52° , and to obtain this freezing point it is necessary either to add some other therapeutically inactive solute if the solution is hypotonic (freezing point above -0.52°) or to dilute the solution if it is hypertonic (freezing point below -0.52°). The usual practice is to add either sodium chloride or dextrose to adjust hypotonic parenteral solutions to isotonicity. Certain solutes, including ammonium chloride, boric acid, urea, glycerin and propylene glycol, cause hemolysis even when they are present in a concentration that is isoosmotic and such solutions obviously are not isotonic. See Appendix A.

In a similar manner solutions intended for ophthalmic use may be adjusted to have a freezing point identical to that of lacrimal fluid, namely, -0.52° . Ophthalmic solutions with higher freezing points usually are made isotonic by the addition of boric acid or sodium chloride.

In laboratories where the necessary equipment is available, the method usually followed for adjusting hypotonic solutions is to determine the freezing-point depression produced by the ingredients of a given prescription or formula, and then to add a quantity of a suitable inert solute calculated to lower the freezing point to -0.52° , whether the solution is for paren-

teral injection or ophthalmic application. A final determination of the freezing-point depression may be made to verify the accuracy of the calculation. If the solution is hypertonic, it must be diluted if an isotonic solution is to be prepared, but it must be remembered that some solutions cannot be diluted without impairing their therapeutic activity. For example, solutions to be used for treating varicose veins require a high concentration of the active ingredient (solute) to make the solution effective. Dilution to isotonic concentration is not indicated in such cases.

Freezing-Point Calculations

As explained in the preceding section, freezing-point data often may be employed in solving problems of isotonicity adjustment. Obviously, the utility of such data is limited to those solutions where the solute does not penetrate the membrane of the tissue, eg, red blood cells, with which it is in contact. In such cases, Appendix A, giving the freezing-point depression of solutions of different concentrations of various substances, provides information essential for solving the problem.

For most substances listed in the table the concentration of an isotonic solution, ie, one that has a freezing point of -0.52° , is given. If this is not listed in the table, it may be determined with sufficient accuracy by simple proportion using, as the basis for calculation, that figure which most nearly produces an isotonic solution. Actually the depression of the freezing point of a solution of an electrolyte is not absolutely proportional to the concentration but varies according to dilution; for example, a solution containing 1 g of procaine hydrochloride in 100 mL has a freezing-point depression of 0.12° , whereas a solution containing 3 g of the same salt in 100 mL has a freezing-point depression of 0.33° , not 0.36° ($3 \times 0.12^\circ$). Since the adjustment to isotonicity need not be absolutely exact, approximations may be made. Nevertheless, adjustments to isotonicity should be as exact as practicable.

Effect of Solvents—Besides water, certain other solvents frequently are employed in nose drops, ear drops and other preparations to be used in various parts of the body. Liquids such as glycerin, propylene glycol or alcohol may compose part of the solvent. In solving isotonicity adjustment problems for such solutions it should be kept in mind that while these solvent components contribute to the freezing-point depression they may or may not have an effect on the "tone" of the tissue to which they are applied, ie, an *isoosmotic* solution may not be *isotonic*. It is apparent that, in such cases, the utility of the methods described above or, for that matter, of any other method of evaluating "tonicity" is questionable.

Tonicity Testing by Observing Erythrocyte Changes

Observation of the behavior of human erythrocytes when suspended in a solution is the ultimate and direct procedure for determining whether the solution is isotonic, hypotonic or hypertonic. If hemolysis or marked change in the appearance of the erythrocytes occurs, the solution is not isotonic with the cells. If the cells retain their normal characteristics, the solution is isotonic.

Hemolysis may occur when the osmotic pressure of the fluid in the erythrocytes is greater than that of the solution in which the cells are suspended, but the specific chemical reactivity of the solute in the solution often is far more important in producing hemolysis than is the osmotic effect. There is no certain evidence that any single mechanism of action causes hemolysis. The process appears to involve such factors as pH, lipid solubility, molecular and ionic sizes of solute particles and possibly inhibition of cholinesterase in cell membranes and denaturing action on plasma membrane protein.

Some investigators test the tonicity of injectable solutions by observing variations of red-blood-cell volume produced by

these solutions. This method appears to be more sensitive to small differences in tonicity than those based on observation of a hemolytic effect. Much useful information concerning the effect of various solutes on erythrocytes has been obtained by this procedure and a summary of many of these data is given in RPS-14, page 1562.

Methods of Adjusting Tonicity

There are several methods for adjusting the tonicity of an aqueous solution provided, of course, that the solution is hypotonic when the drug and additives are dissolved. The most prominent of these methods are the freezing point depression method, the sodium chloride equivalent method and the isotonic solution V-value method. The first two of these methods can be used with a three step problem solving process based on sodium chloride.

1. Identify a reference solution and the associated tonicity parameter.
2. Determine the contribution of the drug(s) and additive(s) to the total tonicity.
3. Determine the amount of sodium chloride needed by subtracting the contribution of the actual solution from the reference solution.

The result of Step 3 also indicates whether the actual solution is hypotonic, isotonic or hypertonic. If the actual solution contributes less to the total tonicity than the reference solution, then the actual solution is hypotonic. If, however, the actual solution contributes a greater amount to tonicity than the reference solution, the actual solution is hypertonic and can be adjusted to isotonicity only by dilution. This may not be possible on therapeutic grounds.

The amount of sodium chloride resulting in Step 3 also can be converted into an amount of other materials, such as dextrose, to render the actual solution isotonic.

Freezing Point Depression Method—The freezing point method makes use of a "D value" (found in Appendix A) which has the units of °C/(x% drug). For example, in Appendix A, dexamethasone sodium phosphate has *D* values of 0.050°C/(0.5% drug), 0.180°C/(2.0% drug), 0.52°C/(6.75% drug), etc. It is apparent that the *D* value is nearly proportional to concentration. If a *D* value is needed for a concentration of drug not listed in Appendix A, a *D* value can be calculated from the Appendix by direct proportion, using a *D* value closest to the concentration of drug in the actual solution.

The reference solution for the freezing point depression method is 0.9% sodium chloride which has a freezing point depression of $\Delta T_f = 0.52^\circ\text{C}$.

Using the three steps described above, the dexamethasone sodium phosphate solution in Example 1 can be rendered isotonic as follows:

Example 1

Dexamethasone Sodium Phosphate	0.1%
Purified Water	qs
Mft Isotonic Solution	30 mL

Step 1—Reference solution: 0.9% sodium chloride.

$$\Delta T_f = 0.52^\circ\text{C}$$

$$D = 0.050^\circ\text{C}/0.5\% \text{ dexamethasone sod phosphate}$$

Step 2—Contribution of drug.

$$\frac{0.050^\circ\text{C}}{0.5\% \text{ drug}} \times 0.1\% \text{ drug} = 0.010^\circ$$

Step 3—Reference solution – actual solution.

$$0.52^\circ - 0.01^\circ = 0.51^\circ$$

Sodium chloride needed.

$$\frac{0.9\% \text{ NaCl}}{0.52^\circ} \times 0.51^\circ = 0.883\% \text{ NaCl}$$

$$\frac{0.883 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.265 \text{ g NaCl}$$

The above solution could be made isotonic with any appropriate material other than sodium chloride by using the *D* value for that material. For example, to make the solution isotonic with dextrose with a *D* value, *D* =

$$0.091^\circ/1\%;$$

$$\frac{1\% \text{ Dextrose}}{0.091^\circ} \times 0.51^\circ = 5.60\% \text{ Dextrose}$$

$$\frac{5.60 \text{ g Dextrose}}{100 \text{ mL}} \times 30 \text{ mL} = 1.68 \text{ g Dextrose}$$

Example 2

Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water	qs
Mft Isotonic solution	30 mL

Step 1—Reference solution: 0.9% sodium chloride.

$$\Delta T_f = 0.52^\circ$$

$$D = 0.14^\circ/1\% \text{ (naphazoline HCl)}$$

$$D = 0.086^\circ/1\% \text{ (zinc sulfate)}$$

Step 2—Contribution of drugs.

$$\frac{0.14^\circ\text{C}}{1\% \text{ N.HCl}} \times 0.02\% \text{ N.HCl} = 0.003^\circ$$

$$\frac{0.086^\circ\text{C}}{1\% \text{ ZnSO}_4} \times 0.25\% \text{ ZnSO}_4 = 0.022^\circ$$

$$0.003^\circ + 0.022^\circ = 0.025^\circ$$

Step 3—Reference solution – actual solution.

$$0.52^\circ - 0.025^\circ = 0.495^\circ$$

Sodium chloride needed.

$$\frac{0.9\% \text{ NaCl}}{0.52^\circ} \times 0.495^\circ = 0.857\% \text{ NaCl}$$

$$\frac{0.857 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.257 \text{ g NaCl}$$

The above solution could be made isotonic with any appropriate material other than sodium chloride by utilizing the *D* value for that material. For example, to make the solution isotonic with dextrose with a *D* value, *D* = 0.091°C/1%;

$$\frac{1\% \text{ Dextrose}}{0.091^\circ} \times 0.495^\circ = 5.44\% \text{ Dextrose}$$

$$\frac{5.44 \text{ g Dextrose}}{100 \text{ mL}} \times 30 \text{ mL} = 1.63 \text{ g Dextrose}$$

Sodium Chloride Equivalent Method—A sodium chloride equivalent, "E value," is defined as the weight of sodium chloride which will produce the same osmotic effect as 1 g of the drug. For example, in Appendix A, dexamethasone sodium phosphate has an *E* value of 0.18 g NaCl/g drug at 0.5% drug concentration, 0.17 g NaCl/g drug at 1% drug concentration and a value of 0.16 g NaCl/g drug at 2% drug. This slight variation in the sodium chloride equivalent with concentration is due to changes in interionic attraction at different concentration of drug; the *E* value is not directly proportional to concentration as was the freezing-point depression.

The reference solution for the sodium chloride equivalent method is 0.9% sodium chloride as it was for the freezing-point depression method.

The dexamethasone sodium phosphate solution in Example 1 can be rendered isotonic using the sodium chloride equivalent method as follows:

Example 1

Dexamethasone Sodium Phosphate	0.1%
Purified Water	qs
Mft Isotonic Solution	30 mL

Step 1—Reference solution: 0.9% sodium chloride.

$$\frac{0.9 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.270 \text{ g NaCl}$$

$$E = 0.18 \text{ g NaCl/g drug}$$

Step 2—Contribution of drug.

$$\frac{0.18 \text{ g NaCl}}{1 \text{ g drug}} \times \frac{0.1 \text{ g drug}}{100 \text{ mL}} \times 30 \text{ mL} = 0.0054 \text{ g NaCl}$$

Step 3—Reference solution – actual solution.

$$0.270 \text{ g NaCl} - 0.0054 \text{ g NaCl} = 0.265 \text{ g NaCl}$$

The above solution can be made isotonic with a material other than sodium chloride, such as dextrose, by using the *E* value of that material. For example, to make the solution isotonic with dextrose, *E* = 0.16 g NaCl/g dextrose, the amount of sodium chloride needed in Step 3, can be converted to dextrose as follows:

$$\frac{1 \text{ g Dextrose}}{0.16 \text{ g NaCl}} \times 0.265 \text{ g NaCl} = 1.66 \text{ g Dextrose}$$

Example 2

Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—Reference solution: 0.9% sodium chloride.

$$\frac{0.9 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.270 \text{ g NaCl}$$

$$E = 0.27 \text{ g NaCl/g N.HCl}$$

$$E = 0.15 \text{ g NaCl/g ZnSO}_4$$

Step 2—Contribution of drugs.

$$\frac{0.27 \text{ g NaCl}}{1 \text{ g N.HCl}} \times \frac{0.02 \text{ g N.HCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.002 \text{ g NaCl}$$

$$\frac{0.15 \text{ g NaCl}}{1 \text{ g ZnSO}_4} \times \frac{0.25 \text{ g ZnSO}_4}{100 \text{ mL}} \times 30 \text{ mL} = 0.011 \text{ g NaCl}$$

$$0.002 \text{ g NaCl} + 0.011 \text{ g NaCl} = 0.013 \text{ g NaCl}$$

Step 3—Reference solution – actual solution.

$$0.270 \text{ g NaCl} - 0.013 \text{ g NaCl} = 0.257 \text{ g NaCl}$$

The above solution can be made isotonic with a material other than sodium chloride, such as dextrose, by using the *E* value of that material. For example, to make the solution isotonic with dextrose, *E* = 0.16 g NaCl/g dextrose, the amount of sodium chloride needed in Step 3 can be converted to dextrose as follows:

$$\frac{1 \text{ g Dextrose}}{0.16 \text{ g NaCl}} \times 0.257 \text{ g NaCl} = 1.61 \text{ g Dextrose}$$

Isotonic Solution V-Values—The “V value” of a drug is the volume of water to be added to a specified weight of drug (0.3 g or 1.0 g depending on the table used) to prepare an isotonic solution. Appendix B gives such values for some commonly used drugs. The reason for providing data for 0.3 g of drug is for convenience in preparing 30 mL (approximately 1 fluidounce) of solution, a commonly prescribed volume. The basic principle underlying the use of V values is to prepare an isotonic solution of the prescribed drug and then dilute this solution to final volume with a suitable isotonic vehicle.

The two solutions in the previous examples can be prepared as follows using the V value method:

Example 1

Dexamethasone Sodium Phosphate	0.1%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—The V value for dexamethasone sodium phosphate can be calculated from the sodium chloride equivalent, *E*, as outlined in the footnote in Appendix B.

$$\frac{100 \text{ mL Soln}}{0.9 \text{ g NaCl}} \times \frac{0.17 \text{ g NaCl}}{1 \text{ g drug}} \times 0.3 \text{ g drug} = 5.67 \text{ mL Soln}$$

for a dilute solution: 5.67 mL Soln = 5.67 mL H₂O

$$\therefore V = (5.67 \text{ mL H}_2\text{O}) / (0.3 \text{ g drug})$$

Step 2—Amount of drug needed.

$$\frac{0.1 \text{ g drug}}{100 \text{ mL}} \times 30 \text{ mL} = 0.030 \text{ g drug}$$

Volume of water needed to prepare an isotonic solution.

$$\frac{5.67 \text{ mL H}_2\text{O}}{0.3 \text{ g drug}} \times 0.030 \text{ g drug} = 0.57 \text{ mL H}_2\text{O}$$

Step 3—To prepare the solution, dissolve 0.030 g of drug in 0.57 mL water, and qs to volume with a suitable isotonic vehicle such as 0.9% sodium chloride solution, 5.51% dextrose or an isotonic phosphate buffer.

Example 2

Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—The V value for naphazoline HCl can be calculated from the sodium chloride equivalent, *E*, as outlined in the footnote in Appendix B; the V value for zinc sulfate is taken directly from Appendix B.

$$\frac{100 \text{ mL Soln}}{0.9 \text{ g NaCl}} \times \frac{0.27 \text{ g NaCl}}{1 \text{ g N.HCl}} \times 0.3 \text{ g N.HCl} = 9.00 \text{ mL Soln}$$

for a dilute solution: 9.00 mL Soln = 9.00 mL H₂O

$$\therefore V = (9.00 \text{ mL H}_2\text{O}) / (0.3 \text{ g N.HCl})$$

$$V = 5.00 \text{ mL H}_2\text{O} / 0.3 \text{ g ZnSO}_4$$

Step 2—Amount of drugs needed.

$$\frac{0.02 \text{ g N.HCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.006 \text{ g N.HCl}$$

$$\frac{0.25 \text{ g ZnSO}_4}{100 \text{ mL}} \times 30 \text{ mL} = 0.075 \text{ g ZnSO}_4$$

Volume of water needed to prepare an isotonic solution.

$$\frac{9.00 \text{ mL H}_2\text{O}}{0.3 \text{ g N.HCl}} \times 0.006 \text{ g drug} = 0.18 \text{ mL H}_2\text{O}$$

$$\frac{5.00 \text{ mL H}_2\text{O}}{0.3 \text{ g ZnSO}_4} \times 0.075 \text{ g ZnSO}_4 = 1.25 \text{ mL H}_2\text{O}$$

$$0.18 \text{ mL H}_2\text{O} + 1.25 \text{ mL H}_2\text{O} = 1.43 \text{ mL H}_2\text{O}$$

Step 3—To prepare the solution, dissolve 0.006 g of naphazoline HCl and 0.075 g zinc sulfate in 1.43 mL water, and qs to volume with a suitable isotonic vehicle such as 0.9% sodium chloride solution, 5.51% dextrose or an isotonic phosphate buffer.

References

- Kaminski MV: *Surg Gyn Obst* 143: 12, 1976.
- Theeuwes F: *J Pharm Sci* 64: 1987, 1975.
- Zenk K, Huxtable RF: *Hosp Pharm* 13: 577, 1978.
- McDuffee L: *IL Council Hosp Pharm Drug Inf Newsl* 8: Oct-Nov, 1978.
- Streng WH, et al.: *J Pharm Sci* 67: 384, 1978.
- Murty BSR, et al.: *Am J Hosp Pharm* 33: 546, 1976.
- Bray AJ: Personal Communication, Mead Johnson Nutritional Division, Evansville IN, 1978.
- Andrassy RJ, et al.: *Surg* 82: 205, 1977.
- Dobbie RP, Hoffmeister JA: *Surg Gyn Obst* 143: 273, 1976.
- Anon, Osmolality: Doyle Pharmaceutical Co, Minneapolis, 1978.
- Dickerson RN, Melnik G: *Am J Hosp Pharm* 45: 832, 1988. Holtz L, Milton J, Sturek JK: *J Parent Ent Nutr* 11: 183, 1987.
- Lund CG, et al.: *The Preparation of Solutions Iso-osmotic with Blood, Tears, and Tissue*. Danish Pharmacopoeial Commission, Einar Munksgaard, Copenhagen, 1947.
- Hammarlund ER, et al.: *J Pharm Sci* 54: 160, 1965.
- Hammarlund ER, Pedersen-Bjergaard K: *J APhA Sci Ed* 47: 107, 1958.
- Hammarlund ER, Pedersen-Bjergaard K: *J Pharm Sci* 50: 24, 1961.
- Hammarlund ER, Van Pevenage GL: *J Pharm Sci* 55: 1448, 1966.
- Sapp C, et al.: *J Pharm Sci* 64: 1884, 1975.
- British Pharmaceutical Codex*, Pharmaceutical Press, London, 1973.
- Fassett WE, et al.: *J Pharm Sci* 58: 1540, 1969.
- Kogan DG, Kinsey VE: *Arch Ophthalmol* 27: 696, 1942.

Bibliography

- Alberty RA, Daniels F: *Physical Chemistry*, 7th ed, Wiley, New York, 1987.
Cowan G, Scheetz W, eds: *Intravenous Hyperalimentation*, Lea & Febiger, Philadelphia, 1972.

- Garb S: *Laboratory Tests in Common Use*, 6th ed, Springer, New York, 1976.
- Hall WE: *Am J Pharm Educ* 34: 204, 1970.
- Harvey AM, Johns RJ, Owens AH, Ross RS: *The Principles and Practice of Medicine*, 18th ed, Appleton-Century-Crofts, New York, 1972.
- Martin AN, Swarbrick J, Cammarata A: *Physical Pharmacy*, 4th ed, Lea & Febiger, Philadelphia, 1993.
- Plumer AL: *Principles and Practice of Intravenous Therapy*, 4th ed, Little, Brown, Boston, 1987.
- Ravel R: *Clinical Laboratory Medicine*, 5th ed, Mosby, St Louis, 1988.
- Shizgal HM: *Ann Rev Med* 42: 549, 1991.
- Tilkian SM, Conover MH: *Clinical Implications of Laboratory Tests*, 4th ed, Mosby, St Louis, 1987.
- Turco S, King RE: *Sterile Dosage Forms*, 3rd ed, Lea & Febiger, Philadelphia, 1987.
- Wallach J: *Interpretation of Diagnostic Tests*, 4th ed, Little, Brown, Boston, 1986.

Appendix A—Sodium Chloride Equivalents, Freezing-Point Depressions and Hemolytic Effects of Certain Medicinals in Aqueous Solution

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a					
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH	
Acetrisoate methylglucamine	0.09		0.08		0.08		0.08		0.08		12.12	0.07		0	7.1	
Acetrisoate sodium	0.10	0.027	0.10	0.055	0.10	0.109	0.10	0.163	0.10	0.273	9.64	0.09	0.52	0	6.9†	
Acetylcysteine	0.20	0.055	0.20	0.113	0.20	0.227	0.20	0.341			4.58	0.20	0.52	100*	2.0	
Adrenaline HCl											4.24			68	4.5	
Alphaprodine HCl	0.19	0.053	0.19	0.105	0.18	0.212	0.18	0.315			4.98	0.18	0.52	100	5.3	
Alum (potassium)			0.18				0.15		0.15		6.35	0.14		24*	3.4	
Amantadine HCl	0.31	0.090	0.31	0.180	0.31	0.354					2.95	0.31	0.52	91	5.7	
Aminoacetic acid	0.42	0.119	0.41	0.235	0.41	0.470					2.20	0.41	0.52	0*	6.2	
Aminohippuric acid	0.13	0.035	0.13	0.075												
Aminophylline				0.098 ^c												
Ammonium carbonate	0.70	0.202	0.70	0.405							1.29	0.70	0.52	97	7.7	
Ammonium chloride			1.12								0.8	1.12	0.52	93	5.0	
Ammonium lactate	0.33	0.093	0.33	0.185	0.33	0.370					2.76	0.33	0.52	98	5.9	
Ammonium nitrate	0.69	0.200	0.69	0.400							1.30	0.69	0.52	91	5.3	
Ammonium phosphate, dibasic	0.53	0.165	0.55	0.315							1.76	0.51	0.52	0	7.9	
Ammonium sulfate	0.55	0.158	0.55	0.315							1.68	0.54	0.52	0	5.3	
Amobarbital sodium			0.25	0.143 ^c			0.25				3.6	0.25	0.52	0	9.3	
d-Amphetamine HCl											2.64			98	5.7	
Amphetamine phosphate			0.34	0.20			0.27	0.47			3.47	0.26	0.52	0	4.5	
Amphetamine sulfate			0.22	0.129 ^c			0.21	0.36			4.23	0.21	0.52	0	5.9	
Amprotropine phosphate											5.90			0	4.2	
Amylcaine HCl			0.22				0.19				4.98	0.18		100	5.6	
Anileridine HCl	0.19	0.052	0.19	0.104	0.19	0.212	0.18	0.316	0.18	0.509	5.13	0.18	0.52	12	2.6	
Antazoline phosphate											6.05			90	4.0	
Antimony potassium tartrate			0.18				0.13		0.10							
Antipyrine			0.17	0.10			0.14	0.24	0.14	0.40	6.81	0.13	0.52	100	6.1	
Apomorphine HCl			0.14	0.080 ^c												
Arginine glutamate	0.17	0.048	0.17	0.097	0.17	0.195	0.17	0.292	0.17	0.487	5.37	0.17	0.52	0	6.9	
Ascorbic acid				0.105 ^c							5.05		0.52 ^b	100*	2.2	
Atropine methylbromide			0.14				0.13		0.13		7.03	0.13				
Atropine methylnitrate											6.52			0	5.2	
Atropine sulfate			0.13	0.075			0.11	0.19	0.11	0.32	8.85	0.10	0.52	0	5.0	
Bacitracin			0.05	0.03			0.04	0.07	0.04	0.12						
Barbital sodium			0.30	0.171 ^c			0.29	0.50			3.12	0.29	0.52	0	9.8	
Benzalkonium chloride			0.16				0.14		0.13							
Benzotropine mesylate	0.26	0.073	0.21	0.115	0.15	0.170	0.12	0.203	0.09	0.242						
Benzyl alcohol			0.17	0.09 ^c			0.15									
Bethanechol chloride	0.50	0.140	0.39	0.225	0.32	0.368	0.30	0.512			3.05	0.30		0	6.0	
Bismuth potassium tartrate			0.09				0.06		0.05							
Bismuth sodium tartrate			0.13				0.12		0.11		8.91	0.10		0	6.1	
Boric acid			0.50	0.288 ^c							1.9	0.47	0.52	100	4.6	
Brompheniramine maleate	0.10	0.026	0.09	0.050	0.08	0.084										
Bupivacaine HCl	0.17	0.048	0.17	0.096	0.17	0.193	0.17	0.290	0.17	0.484	5.38	0.17	0.52	83	6.8	
Butabarbital sodium	0.27	0.078	0.27	0.155	0.27	0.313	0.27	0.470			3.33	0.27	0.52	0	6.8	
Butacaine sulfate			0.20	0.12			0.13	0.23	0.10	0.29						
Caffeine and sodium benzoate			0.26	0.15			0.23	0.40			3.92	0.23	0.52	0	7.0	
Caffeine and sodium salicylate			0.12	0.12			0.17	0.295	0.16	0.46	5.77	0.16	0.52	0	6.8	
Calcium aminosaliclate											4.80			0	6.0	
Calcium chloride			0.51	0.298 ^c							1.70	0.53	0.52	0	5.6	
Calcium chloride (6 H ₂ O)			0.35	0.20							2.5	0.36	0.52	0	5.7	
Calcium chloride, anhydrous			0.68	0.39							1.3	0.69	0.52	0	5.6	
Calcium disodium edetate	0.21	0.061	0.21	0.120	0.21	0.240	0.20	0.357			4.50	0.20	0.52	0	6.1	
Calcium gluconate			0.16	0.091 ^c			0.14	0.24								
Calcium lactate			0.23	0.13			0.12	0.36			4.5	0.20	0.52	0	6.7	
Calcium lactobionate	0.08	0.022	0.08	0.043	0.08	0.085	0.07	0.126	0.07	0.197						
Calcium levulinate			0.27	0.16			0.25	0.43			3.58			0	7.2	
Calcium pantothenate											5.50			0	7.4	
Camphor				0.12 ^d												
Capreomycin sulfate	0.04	0.011	0.04	0.020	0.04	0.042	0.04	0.063	0.04	0.106				0	5.9	
Carbachol				0.205 ^c							2.82			0	5.9	
Carbenicillin sodium	0.20	0.059	0.20	0.118	0.20	0.236	0.20	0.355			4.40	0.20	0.52	0	6.6	
Carboxymethylcellulose sodium	0.03	0.007	0.03	0.017	0.145											

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a					pH
	E	D	E	D	E	D	E	D	E	D	%	E	D	H		
Cephaloridine	0.09	0.023	0.07	0.041	0.06	0.074	0.06	0.106	0.05							
Chloramine-T											4.10			100*		9.1
Chloramphenicol				0.06 ^d												
Chloramphenicol sodium succinate	0.14	0.038	0.14	0.078	0.14	0.154	0.13	0.230	0.13	0.382	6.83	0.13	0.52	partial		6.1
Chlordiazepoxide HCl	0.24	0.068	0.22	0.125	0.19	0.220	0.18	0.315	0.17	0.487	5.50	0.16	0.52	66		2.7
Chlorobutanol (hydrated)				0.24 0.14												
Chloroprocaine HCl	0.20	0.054	0.20	0.108	0.18	0.210										
Chloroquine phosphate	0.14	0.039	0.14	0.082	0.14	0.162	0.14	0.242	0.13	0.379	7.15	0.13	0.52	0		4.3
Chloroquine sulfate	0.10	0.028	0.09	0.050	0.08	0.090	0.07	0.127	0.07	0.195						
Chlorpheniramine maleate	0.17	0.048	0.15	0.085	0.14	0.165	0.13	0.220	0.09	0.265						
Chlortetracycline HCl	0.10	0.030	0.10	0.061	0.10	0.121										
Chlortetracycline sulfate				0.13 0.08			0.10	0.17								
Citric acid				0.18 0.10			0.17	0.295	0.16	0.46	5.52	0.16	0.52	100*		1.8
Clindamycin phosphate	0.08	0.022	0.08	0.046	0.08	0.095	0.08	0.144	0.08	0.242	10.73	0.08	0.52	58*		6.8
Cocaine HCl				0.16 0.090 ^c			0.15	0.26	0.14	0.40	6.33	0.14	0.52	47		4.4
Codeine phosphate				0.14 0.080 ^c			0.13	0.23	0.13	0.38	7.29	0.12	0.52	0		4.4
Colistimethate sodium	0.15	0.045	0.15	0.085	0.15	0.170	0.15	0.253	0.14	0.411	6.73	0.13	0.52	0		7.6
Cupric sulfate				0.18 0.100 ^c			0.15		0.14		6.85	0.13		trace*		3.9
Cyclizine HCl	0.20	0.060														
Cyclophosphamide	0.10	0.031	0.10	0.061	0.10	0.125										
Cytarabine	0.11	0.034	0.11	0.066	0.11	0.134	0.11	0.198	0.11	0.317	8.92	0.10	0.52	0		8.0
Deferoxamine mesylate	0.09	0.023	0.09	0.047	0.09	0.093	0.09	0.142	0.09	0.241						
Demecarium bromide	0.14	0.038	0.12	0.069	0.10	0.108	0.08	0.139	0.07	0.192						
Dexamethasone sodium phosphate	0.18	0.050	0.17	0.095	0.16	0.180	0.15	0.260	0.14	0.410	6.75	0.13	0.52	0		8.9
Dextroamphetamine HCl	0.34	0.097	0.34	0.196	0.34	0.392					2.64	0.34	0.52			
Dextroamphetamine phosphate				0.25 0.14			0.25	0.44			3.62	0.25	0.52	0		4.7
Dextroamphetamine sulfate	0.24	0.069	0.23	0.134	0.22	0.259	0.22	0.380			4.16	0.22	0.52	0		5.9
Dextrose				0.16 0.091 ^c			0.16	0.28	0.16	0.46	5.51	0.16	0.52	0		5.9
Dextrose (anhydrous)				0.18 0.101 ^c			0.18	0.31			5.05	0.18	0.52	0		6.0
Diatrizoate sodium	0.10	0.025	0.09	0.049	0.09	0.098	0.09	0.149	0.09	0.248	10.55	0.09	0.52	0		7.9
Dibucaine HCl				0.074 ^c												
Dicloxacillin sodium (1 H ₂ O)	0.10	0.030	0.10	0.061	0.10	0.122	0.10	0.182								
Diethanolamine	0.31	0.089	0.31	0.177	0.31	0.358					2.90	0.31	0.52	100		11.3
Dihydrostreptomycin sulfate				0.06 0.03			0.05	0.09	0.05	0.14	19.4	0.05	0.52	0		6.1
Dimethylpyridine maleate	0.13	0.039	0.12	0.070	0.11	0.120										
Dimethyl sulfoxide	0.42	0.122	0.42	0.245	0.42	0.480					2.16	0.42	0.52	100		7.6
Diperodon HCl	0.15	0.045	0.14	0.079	0.13	0.141										
Diphenhydramine HCl				0.161 ^c							5.70			88*		5.5
Diphenidol HCl	0.16	0.045	0.16	0.09	0.16	0.180										
Doxapram HCl	0.12	0.035	0.12	0.070	0.12	0.140	0.12	0.210								
Doxycycline hyclate	0.12	0.035	0.12	0.072	0.12	0.134	0.11	0.186	0.09	0.264						
Dyphylline	0.10	0.025	0.10	0.052	0.09	0.104	0.09	0.155	0.08	0.245						
Echothiophate iodide	0.16	0.045	0.16	0.090	0.16	0.179										
Edetate disodium	0.24	0.070	0.23	0.132	0.22	0.248	0.21	0.360			4.44	0.20	0.52	0		4.7
Edetate trisodium monohydrate	0.29	0.079	0.29	0.158	0.28	0.316	0.27	0.472			3.31	0.27	0.52	0		8.0
Emetine HCl				0.058 ^c			0.17		0.29							
Ephedrine HCl				0.30 0.165 ^c			0.28				3.2	0.28		96		5.9
Ephedrine sulfate				0.23 0.13			0.20	0.35			4.54	0.20	0.52	0		5.7
Epinephrine bitartrate				0.18 0.104			0.16	0.28	0.16	0.462	5.7	0.16	0.52	100*		3.4
Epinephrine hydrochloride				0.29 0.16 ^b			0.26				3.47	0.26				
Ergonovine maleate				0.089 ^c												
Erythromycin lactobionate	0.08	0.020	0.07	0.040	0.07	0.078	0.07	0.115	0.06	0.187						
Ethyl alcohol											1.39			100		6.0
Ethylenediamine				0.253 ^c							2.08			100*		11.4
Ethylmorphine HCl			0.16	0.088 ^c			0.15	0.26	0.15	0.43	6.18	0.15	0.52	38		4.7
Eucatropine HCl				0.11 ^d												
Ferric ammonium citrate (green)											6.83			0		5.2
Floxuridine	0.14	0.040	0.13	0.076	0.13	0.147	0.12	0.213	0.12	0.335	8.47	0.12	0.52	3*		4.5
Fluorescein sodium				0.31 0.181 ^c			0.27	0.47			3.34	0.27	0.52	0		8.7
Fluphenazine 2-HCl	0.14	0.041	0.14	0.082	0.12	0.145	0.09	0.155								
d-Fructose											5.05			0*		5.9
Furthronium iodide	0.24	0.070	0.24	0.133	0.22	0.250	0.21	0.360			4.44	0.20	0.52	0		5.4
Galactose											4.92			0		5.9
Gentamicin sulfate	0.05	0.015	0.05	0.030	0.05	0.060	0.05	0.093	0.05	0.153						
D-Glucuronic acid											5.02			48*		1.6
Glycerin				0.203 ^c							2.6			100		5.9
Glycopyrrolate	0.15	0.042	0.15	0.084	0.15	0.166	0.14	0.242	0.13	0.381	7.22	0.12	0.52	92*		4.0
Gold sodium thiomalate	0.10	0.032	0.10	0.061	0.10	0.111	0.09	0.159	0.09	0.250						
Hetacillin potassium	0.17	0.048	0.17	0.095	0.17	0.190	0.17	0.284	0.17	0.474	5.50	0.17	0.52	0		6.3
Hexafluorenum bromide	0.12	0.033	0.11	0.065												
Hexamethonium tartrate	0.16	0.045	0.16	0.089	0.16	0.181	0.16	0.271	0.16	0.456	5.68	0.16	0.52			
Hexamethylene sodium acetaminosalicylate	0.18	0.049	0.18	0.099	0.17	0.199	0.17	0.297	0.16	0.485	5.48	0.16	0.52	0*		4.0

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ¹⁹				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Hexobarbital sodium				0.15 ^c											
Hexylcaine HCl											4.30			100	4.8
Histamine 2HCl	0.40	0.115	0.40	0.233	0.40	0.466					2.24	0.40	0.52	79 *	3.7
Histamine phosphate				0.149 ^c							4.10			0	4.6
Histidine HCl											3.45			40	3.9
Holocaine HCl			0.20	0.12											
Homatropine hydrobromide			0.17	0.097 ^c			0.16	0.28	0.16	0.46	5.67	0.16	0.52	92	5.0
Homatropine methylbromide			0.19	0.11			0.15	0.26	0.13	0.38					
4-Homosulfanilamide HCl											3.69			0	4.9
Hyaluronidase	0.01	0.004	0.01	0.007	0.01	0.013	0.01	0.020	0.01	0.033					
Hydromorphone HCl											6.39			64	5.6
Hydroxyamphetamine HBr				0.15 ^d							3.71			92	5.0
8-Hydroxyquinoline sulfate											9.75			59 *	2.5
Hydroxystilbamidine isethionate	0.20	0.060	0.16	0.090	0.12	0.137	0.10	0.170	0.07	0.216					
Hyoscyamine hydrobromide											6.53			68	5.9
Imipramine HCl	0.20	0.058	0.20	0.110	0.13	0.143									
Indigotindisulfonate sodium	0.30	0.085	0.30	0.172											
Intracaine HCl											4.97			85	5.0
Iodophthalein sodium				0.07 ^c							9.58			100	9.4
Isoamethoptene mucate	0.18	0.048	0.18	0.095	0.18	0.196	0.18	0.302			4.95	0.18	0.52	0	6.2
Isoproterenol sulfate	0.14	0.039	0.14	0.078	0.14	0.156	0.14	0.234	0.14	0.389	6.65	0.14	0.52	trace	4.5
Kanamycin sulfate	0.08	0.021	0.07	0.041	0.07	0.083	0.07	0.125	0.07	0.210					
Lactic acid				0.239 ^c							2.30			100*	2.1
Lactose			0.07	0.040 ^c			0.08		0.09		9.75	0.09		0*	5.8
Levallorphan tartrate	0.13	0.036	0.13	0.073	0.13	0.143	0.12	0.210	0.12	0.329	9.40	0.10	0.52	59*	6.9
Levorphanol tartrate	0.12	0.033	0.12	0.067	0.12	0.136	0.12	0.203							
Lidocaine HCl				0.13 ^c							4.42			85	4.3
Lircomycin HCl	0.16	0.045	0.16	0.090	0.15	0.170	0.14	0.247	0.14	0.400	6.60	0.14	0.52	0	4.5
Lobeline HCl				0.09 ^b											
Lyapolate sodium	0.10	0.025	0.09	0.051	0.09	0.103	0.09	0.157	0.09	0.263	9.96	0.09	0.52	0	6.5†
Magnesium chloride				0.45							2.02	0.45		0	6.3
Magnesium sulfate			0.17	0.094 ^c			0.15	0.26	0.15	0.43	6.3	0.14	0.52	0	6.2
Magnesium sulfate, anhydrous	0.34	0.093	0.32	0.184	0.30	0.345	0.29	0.495			3.18	0.28	0.52	0	7.0
Mannitol				0.098 ^c					5.07					0*	6.2
Maphenide HCl	0.27	0.075	0.27	0.153	0.27	0.303	0.26	0.448			3.55	0.25	0.52		
Menadiol sodium diphosphate											4.36			0	8.2
Menadione sodium bisulfite											5.07			0	5.3
Menthol				0.12 ^d											
Meperidine HCl				0.125 ^c							4.80			98	5.0
Mepivacaine HCl	0.21	0.060	0.21	0.116	0.20	0.230	0.20	0.342			4.60	0.20	0.52	45	4.5
Merbromin				0.08 ^b											
Mercuric cyanide			0.15				0.14		0.13						
Mersalyl				0.06 ^b											
Mesoridazine besylate	0.10	0.024	0.07	0.040	0.05	0.058	0.04	0.071	0.03	0.087					
Metaraminol bitartrate	0.20	0.060	0.20	0.112	0.19	0.210	0.18	0.308	0.17	0.505	5.17	0.17	0.52	59	3.8
Methacholine chloride				0.184 ^c							3.21			0	4.5
Methadone HCl				0.101 ^c							8.59			100*	5.0
Methamphetamine HCl				0.213 ^c							2.75			97	5.9
Methdilazine HCl	0.12	0.035	0.10	0.056	0.08	0.080	0.06	0.093	0.04	0.112					
Methenamine			0.23				0.24				3.68	0.25		100	8.4
Methiodal sodium	0.24	0.068	0.24	0.136	0.24	0.274	0.24	0.410			3.81	0.24	0.52	0	5.9
Methitural sodium	0.26	0.074	0.25	0.142	0.24	0.275	0.23	0.407			3.85	0.23	0.52	78	9.8
Methocarbamol	0.10	0.030	0.10	0.060											
Methotrimeprazine HCl	0.12	0.034	0.10	0.060	0.07	0.077	0.06	0.094	0.04	0.125					
Methoxyphenamine HCl	0.26	0.075	0.26	0.150	0.26	0.300	0.26	0.450			3.47	0.26	0.52	96	5.4
p-Methylaminoethanolphenol tartrate	0.18	0.048	0.17	0.095	0.16	0.190	0.16	0.282	0.16	0.453	5.83	0.16	0.52	0	6.2
Methyldopate HCl	0.21	0.063	0.21	0.122	0.21	0.244	0.21	0.365			4.28	0.21	0.52	partial	3.0
Methylergonovine maleate	0.10	0.028	0.10	0.056											
N-Methylglucamine	0.20	0.057	0.20	0.111	0.18	0.214	0.18	0.315	0.18	0.517	5.02	0.18	0.52	4	11.3
Methylphenidate HCl	0.22	0.065	0.22	0.127	0.22	0.258	0.22	0.388			4.07	0.22	0.52	66	4.3
Methylprednisolone Na succinate	0.10	0.025	0.09	0.051	0.09	0.102	0.08	0.143	0.07	0.200					
Minocycline HCl	0.10	0.030	0.10	0.058	0.09	0.107	0.08	0.146							
Monoethanolamine	0.53	0.154	0.53	0.306							1.70	0.53	0.52	100	11.4
Morphine HCl			0.15	0.086 ^c			0.14								
Morphine sulfate			0.14	0.079 ^c			0.11	0.19	0.09	0.26					
Nalorphine HCl	0.24	0.070	0.21	0.121	0.18	0.210	0.17	0.288	0.15	0.434	6.36	0.14	0.52	63	4.1
Naloxone HCl	0.14	0.042	0.14	0.083	0.14	0.158	0.13	0.230	0.13	0.367	8.07	0.11	0.52	35	5.2
Naphazoline HCl			0.27	0.14 ^d			0.24				3.99	0.22		100	5.3
Neosarsphenamine											2.32			17	7.8
Neomycin sulfate			0.11	0.063 ^c			0.09	0.16	0.08	0.232					
Neostigmine bromide			0.22	0.127 ^c			0.19				4.98			0	4.6
Neostigmine methylsulfate			0.20	0.115 ^c			0.18		0.17		5.22	0.17			

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Nicotinamide			0.26	0.148 ^c			0.21	0.36			4.49	0.20	0.52	100	7.0
Nicotinic acid			0.26	0.144 ^c											
Nikethamide				0.100 ^c							5.94			100	6.9
Novobiocin sodium	0.12	0.033	0.10	0.057	0.07	0.073									
Oleandomycin phosphate	0.08	0.017	0.08	0.038	0.08	0.084	0.08	0.129	0.08	0.255	10.82	0.08	0.52	0	5.0
Orphenadrine citrate	0.13	0.037	0.13	0.074	0.13	0.144	0.12	0.204	0.10	0.285					
Oxophenarsine HCl											3.67			trace*	2.3
Oxymetazoline HCl	0.22	0.063	0.22	0.124	0.20	0.232	0.19	0.335			4.92	0.18	0.52	86	5.7
Oxyquinoline sulfate	0.24	0.068	0.21	0.113	0.16	0.182	0.14	0.236	0.11	0.315					
d-Pantothenyl alcohol	0.20	0.053	0.18	0.100	0.17	0.193	0.17	0.283	0.16	0.468	5.60	0.16	0.52	92	6.8
Papaverine HCl			0.10	0.061 ^c											
Paraldehyde	0.25	0.071	0.25	0.142	0.25	0.288	0.25	0.430			3.65	0.25	0.52	97	5.3
Pargyline HCl	0.30	0.083	0.29	0.165	0.29	0.327	0.28	0.491			3.18	0.28	0.52	91	3.8
Penicillin G, potassium			0.18	0.102 ^c			0.17	0.29	0.16	0.46	5.48	0.16	0.52	0	6.2
Penicillin G, procaine				0.06 ^d											
Penicillin G, sodium			0.18	0.100 ^c			0.16	0.28	0.16	0.46	5.90			18	5.2
Pentazocine lactate	0.15	0.042	0.15	0.085	0.15	0.169	0.15	0.253	0.15	0.420					
Pentobarbital sodium				0.145 ^c							4.07			0	9.9
Pentolinium tartrate											5.95			55*	3.4
Phenacaine HCl				0.09 ^d											
Pheniramine maleate				0.09 ^d											
Phenobarbital sodium			0.24	0.135 ^c			0.23	0.40			3.95	0.23	0.52	0	9.2
Phenol			0.35	0.20							2.8	0.32	0.52	0*	5.6
Phentolamine mesylate	0.18	0.052	0.17	0.096	0.16	0.173	0.14	0.244	0.13	0.364	8.23	0.11	0.52	83	3.5
Phenylephrine HCl			0.32	0.184 ^c			0.30				3.0	0.30		0	4.5
Phenylephrine tartrate											5.90			58*	5.4
Phenylethyl alcohol	0.25	0.070	0.25	0.141	0.25	0.283									
Phenylpropanolamine HCl			0.38	0.219 ^c							2.6	0.35		95	5.3
Physostigmine salicylate			0.16	0.090 ^c											
Physostigmine sulfate				0.074 ^c											
Pilocarpine HCl			0.24	0.138 ^c			0.22	0.38			4.08	0.22	0.52	89	4.0
Pilocarpine nitrate			0.23	0.132 ^c			0.20	0.35			4.84	0.20	0.52	88	3.9
Piperocaine HCl				0.12 ^d							5.22			65	5.7
Polyethylene glycol 300	0.12	0.034	0.12	0.069	0.12	0.141	0.12	0.216	0.13	0.378	6.73	0.13	0.52	53	3.8
Polyethylene glycol 400	0.08	0.022	0.08	0.047	0.09	0.098	0.09	0.153	0.09	0.272	8.50	0.11	0.52	0	4.4
Polyethylene glycol 1500	0.06	0.015	0.06	0.036	0.07	0.078	0.07	0.120	0.07	0.215	10.00	0.09	0.52	4	4.1
Polyethylene glycol 1540	0.02	0.005	0.02	0.012	0.02	0.028	0.03	0.047	0.03	0.094					
Polyethylene glycol 4000	0.02	0.004	0.02	0.008	0.02	0.020	0.02	0.033	0.02	0.067					
Polymyxin B sulfate			0.09	0.052			0.06	0.10	0.04	0.12					
Polysorbate 80	0.02	0.005	0.02	0.010	0.02	0.020	0.02	0.032	0.02	0.055					
Polyvinyl alcohol (99% hydrol)	0.02	0.004	0.02	0.008	0.02	0.020	0.02	0.035	0.03	0.075					
Polyvinylpyrrolidone	0.01	0.003	0.01	0.006	0.01	0.010	0.01	0.017	0.01	0.035					
Potassium acetate	0.59	0.172	0.59	0.342							1.53	0.59	0.52	0	7.6
Potassium chlorate											1.88			0	6.9
Potassium chloride			0.76	0.439 ^c							1.19	0.76	0.52	0	5.9
Potassium iodide			0.34	0.196 ^c							2.59	0.34	0.52	0	7.0
Potassium nitrate			0.56	0.324 ^c							1.62	0.56		0	5.9
Potassium phosphate			0.46	0.27							2.08	0.43	0.52	0	8.4
Potassium phosphate, monobasic			0.44	0.25							2.18	0.41	0.52	0	4.4
Potassium sulfate			0.44								2.11	0.43		0	6.6
Pralidoxime chloride	0.32	0.092	0.32	0.183	0.32	0.364					2.87	0.32	0.52	0	4.6
Prilocaine HCl	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.375			4.18	0.22	0.52	45	4.6
Procainamide HCl			0.22	0.13			0.19	0.33	0.17	0.49					
Procaine HCl			0.21	0.122 ^c			0.19	0.33	0.18		5.05	0.18	0.52	91	5.6
Prochlorperazine edisylate	0.08	0.020	0.06	0.033	0.05	0.048	0.03	0.056	0.02	0.065					
Promazine HCl	0.18	0.050	0.13	0.077	0.09	0.102	0.07	0.112	0.05	0.137					
Proparacaine HCl	0.16	0.044	0.15	0.086	0.15	0.169	0.14	0.247	0.13	0.380	7.46	0.12	0.52		
Propiomazine HCl	0.18	0.050	0.15	0.084	0.12	0.133	0.10	0.165	0.08	0.215					
Propoxycaïne HCl											6.40			16	5.3
Propylene glycol											2.00			100	5.5
Pyrathiazine HCl	0.22	0.065	0.17	0.095	0.11	0.123	0.08	0.140	0.06	0.170					
Pyridostigmine bromide	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.377			4.13	0.22	0.52	0	7.2
Pyridoxine HCl											3.05			31*	3.2
Quinacrine methanesulfonate				0.06 ^c			0.09	0.16							
Quinine bisulfate			0.09	0.05			0.19	0.33	0.18		5.07	0.18	0.52	trace*	2.5
Quinine dihydrochloride			0.23	0.130 ^c			0.11	0.19							
Quinine hydrochloride			0.14	0.077 ^c			0.21	0.36			4.5	0.20	0.52	64	2.9
Quinine and urea HCl			0.23	0.13							3.30			96	5.0
Resorcinol				0.161 ^c											
Rolitetraacycline	0.11	0.032	0.11	0.064	0.10	0.113	0.09	0.158	0.07	0.204					
Rose Bengal	0.08	0.020	0.07	0.040	0.07	0.083	0.07	0.124	0.07	0.198	14.9	0.06	0.52		
Rose Bengal B	0.08	0.022	0.08	0.044	0.08	0.087	0.08	0.131	0.08	0.218					
Scopolamine HBr			0.12	0.07			0.12	0.21	0.12	0.35	7.85	0.11	0.52	8	4.8
Scopolamine methylnitrate			0.16				0.14		0.13		6.95	0.13		0	6.0

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Secobarbital sodium			0.24	0.14			0.23	0.40			3.9	0.23	0.52	trace	9.8
Silver nitrate			0.33	0.190 ^c							2.74	0.33	0.52	0*	5.0
Silver protein, mild			0.17	0.10			0.17	0.29	0.16	0.46	5.51	0.16	0.52	0	9.0
Silver protein, strong				0.06 ^d											
Sodium acetate			0.46	0.267							2.0	0.45	0.52		
Sodium acetazolamide	0.24	0.068	0.23	0.135	0.23	0.271	0.23	0.406			3.85	0.23	0.52		
Sodium aminosalicylate				0.170 ^c							3.27			0	7.3
Sodium ampicillin	0.16	0.045	0.16	0.090	0.16	0.181	0.16	0.072	0.16	0.451	5.78	0.16	0.52	0	8.5
Sodium ascorbate											3.00			0	6.9
Sodium benzoate			0.40	0.230 ^c							2.25	0.40	0.52	0	7.5
Sodium bicarbonate			0.65	0.375							1.39	0.65	0.52	0	8.3
Sodium biphosphate (H ₂ O)			0.40	0.23							2.45	0.37	0.52	0	4.1
Sodium biphosphate (2 H ₂ O)			0.36								2.77	0.32		0	4.0
Sodium bismuth thioglycollate	0.20	0.055	0.19	0.107	0.18	0.208	0.18	0.303	0.17	0.493	5.29			0	8.3
Sodium bisulfite			0.61	0.35							1.5	0.61	0.52	0*	3.0
Sodium borate			0.42	0.241 ^c							2.6	0.35	0.52	0	9.2
Sodium bromide											1.60			0	6.1
Sodium cacodylate			0.32				0.28				3.3	0.27		0	8.0
Sodium carbonate, monohydrated			0.60	0.346							1.56	0.58	0.52	100	11.1
Sodium cephalothin	0.18	0.050	0.17	0.095	0.16	0.179	0.15	0.259	0.14	0.400	6.80	0.13	0.52	partial	8.5
Sodium chloride			1.00	0.576 ^c			1.00	1.73	1.00	2.88	0.9	1.00	0.52	0	6.7
Sodium citrate			0.31	0.178 ^c			0.30	0.52			3.02	0.30		0	7.8
Sodium colistimethate	0.16	0.045	0.15	0.087	0.14	0.161	0.14	0.235	0.13	0.383	6.85	0.13	0.52	0	8.4
Sodium hypophosphite											1.60			0	7.3
Sodium iodide			0.39	0.222 ^c							2.37	0.38	0.52	0	6.9
Sodium iodohippurate											5.92			0	7.3
Sodium lactate											1.72			0	6.5
Sodium lauryl sulfate	0.10	0.029	0.08	0.046	0.07	0.068	0.05	0.086			5.30			0	8.4
Sodium mercaptomerin											1.38	0.65	0.52	5*	4.5
Sodium metabisulfite			0.67	0.386 ^c							6.00	0.15	0.52	0	5.8
Sodium methicillin	0.18	0.050	0.18	0.099	0.17	0.192	0.16	0.281	0.15	0.445					
Sodium nafcillin	0.14	0.039	0.14	0.078	0.14	0.158	0.13	0.219	0.10	0.285					
Sodium nitrate			0.68								1.36	0.66		0	6.0
Sodium nitrite			0.84	0.480 ^c							1.08	0.83		0*	8.5
Sodium oxacillin	0.18	0.050	0.17	0.095	0.16	0.177	0.15	0.257	0.14	0.408	6.64	0.14	0.52	0	6.0
Sodium phenylbutazone	0.19	0.054	0.18	0.104	0.17	0.202	0.17	0.298	0.17	0.488	5.34	0.17	0.52		
Sodium phosphate			0.29	0.168			0.27	0.47			3.33	0.27	0.52	0	9.2
Sodium phosphate, dibasic, (2 H ₂ O)			0.42	0.24							2.23	0.40	0.52	0	9.2
Sodium phosphate, dibasic (12 H ₂ O)			0.22				0.21				4.45	0.20		0	9.2
Sodium propionate			0.61	0.35							1.47	0.61	0.52	0	7.8
Sodium salicylate			0.36	0.210 ^c							2.53	0.36	0.52	0	6.7
Sodium succinate	0.32	0.092	0.32	0.184	0.31	0.361					2.90	0.31	0.52	0	8.5
Sodium sulfate, anhydrous			0.58	0.34							1.61	0.56	0.52	0	6.2
Sodium sulfite, exsiccated			0.65	0.38							1.45			0	9.6
Sodium sulfobromophthalein	0.07	0.019	0.06	0.034	0.05	0.060	0.05	0.084	0.04	0.123					
Sodium tartrate	0.33	0.098	0.33	0.193	0.33	0.385					2.72	0.33	0.52	0	7.3
Sodium thiosulfate			0.31	0.181 ^c							2.98	0.30	0.52	0	7.4
Sodium warfarin	0.18	0.049	0.17	0.095	0.16	0.181	0.15	0.264	0.15	0.430	6.10	0.15	0.52	0	8.1
Sorbitol (½ H ₂ O)											5.48			0	5.9
Sparteine sulfate	0.10	0.030	0.10	0.056	0.10	0.111	0.10	0.167	0.10	0.277	9.46	0.10	0.52	19*	3.6
Spectinomycin HCl	0.16	0.045	0.16	0.092	0.16	0.185	0.16	0.280	0.16	0.460	5.66	0.16	0.52	3	4.4
Streptomycin HCl			0.17	0.10 ^c			0.16	0.16							
Streptomycin sulfate			0.07	0.036 ^c			0.06	0.10	0.06	0.17					
Sucrose			0.08	0.047 ^c			0.09	0.16	0.09	0.26	9.25	0.10	0.52	0	6.4
Sulfacetamide sodium			0.23	0.132 ^c			0.23	0.40			3.85	0.23	0.52	0	8.7
Sulfadiazine sodium			0.24	0.14			0.24	0.38			4.24	0.21	0.52	0	9.5
Sulfamerazine sodium			0.23	0.13			0.21	0.36			4.53	0.20	0.52	0	9.8
Sulfapyridine sodium			0.23	0.13			0.21	0.36			4.55	0.20	0.52	5	10.4
Sulfathiazole sodium			0.22	0.13			0.20	0.35			4.82	0.19	0.52	0	9.9
Tartaric acid				0.143 ^c							3.90			75*	1.7
Tetracaine HCl			0.18	0.109 ^c			0.15	0.26	0.12	0.35					
Tetracycline HCl			0.14	0.081 ^c			0.10								
Tetrahydrozoline HCl											4.10			60*	6.7
Theophylline			0.02 ^b												
Theophylline sodium glycinate											2.94			0	8.9
Thiamine HCl			0.139 ^c								4.24			87*	3.0
Thiethylperazine maleate	0.10	0.030	0.09	0.050	0.08	0.089	0.07	0.119	0.05	0.153					
Thiopental sodium				0.155 ^c							3.50			74	10.3
Thiopropazate diHCl	0.20	0.053	0.16	0.090	0.12	0.137	0.10	0.170	0.08	0.222					
Thioridazine HCl	0.06	0.015	0.05	0.025	0.04	0.042	0.03	0.055	0.03	0.075					
Thiotepa	0.16	0.045	0.16	0.090	0.16	0.182	0.16	0.278	0.16	0.460	5.67	0.16	0.52	10*	8.2
Tridihexethyl chloride	0.16	0.047	0.16	0.096	0.16	0.191	0.16	0.280	0.16	0.463	5.62	0.16	0.52	97	5.4
Triethanolamine	0.20	0.058	0.21	0.121	0.22	0.252	0.22	0.383			4.05	0.22	0.52	100	10.7
Trifluoperazine 2HCl	0.18	0.052	0.18	0.100	0.13	0.144									
Triflupromazine HCl	0.10	0.031	0.09	0.051	0.05	0.061	0.04	0.073	0.03	0.092					

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Triepazine tartrate	0.10	0.023	0.06	0.035	0.04	0.045	0.03	0.052	0.02	0.061					
Trimethadione	0.23	0.069	0.23	0.133	0.22	0.257	0.22	0.378			4.22	0.21	0.52	100	6.0
Trimethobenzamide HCl	0.12	0.033	0.10	0.062	0.10	0.108	0.09	0.153	0.08	0.232					
Tripeleminamine HCl				0.13 ^d							5.50			100	6.3
Tromethamine	0.26	0.074	0.26	0.150	0.26	0.300	0.26	0.450			3.45	0.26	0.52	0	10.2
Tropicamide	0.10	0.030	0.09	0.050											
Trypan blue	0.26	0.075	0.26	0.150											
Tryparsamide				0.11 ^c											
Tubocurarine chloride				0.076 ^c											
Urea			0.59	0.34							1.63	0.55	0.52	100	6.6
Urethan				0.18 ^b							2.93			100	6.3
Uridine	0.12	0.035	0.12	0.069	0.12	0.138	0.12	0.208	0.12	0.333	8.18	0.11	0.52	0*	6.1
Valethamate bromide	0.16	0.044	0.15	0.085	0.15	0.168	0.14	0.238	0.11	0.324					
Vancomycin sulfate	0.06	0.015	0.05	0.028	0.04	0.049	0.04	0.066	0.04	0.098					
Viomycin sulfate			0.08	0.05			0.07	0.12	0.07	0.20					
Xylometazoline HCl	0.22	0.065	0.21	0.121	0.20	0.232	0.20	0.342			4.68	0.19	0.52	88	5.0
Zinc phenolsulfonate											5.40			0*	5.4
Zinc sulfate			0.15	0.086 ^c			0.13	0.23	0.12	0.35	7.65	0.12	0.52		

^a The unmarked values were taken from Hammarlund et al.¹³⁻¹⁶ and Sapp et al.¹⁷^b Adapted from Lund et al.¹²^c Adapted from BPC.¹⁸^d Obtained from several sources.

^e E: sodium chloride equivalents. D: freezing-point depression, °C. H: hemolysis, %, at the concentration which is iso-osmotic with 0.9% NaCl, based on freezing-point determination or equivalent test. pH: approximate pH of solution studied for hemolytic action. *: change in appearance of erythrocytes and/or solution.^{17-19†} pH determined after addition of blood.

NB—See also, Budavari S, ed: *Merck Index*, 11th ed, Merck & Co, Rahway NJ, 1988; pp MISC 79-103.Appendix B—Isotonic Solution V-Values^{20a,b}

Drug (0.3 g)	Water needed for isotonicity, mL	Drug (0.3 g)	Water needed for isotonicity, mL	Drug (0.3 g)	Water needed for isotonicity, mL
Alcohol	21.7	Epinephrine hydrochloride	9.7	Silver nitrate	11.0
Anonium chloride	37.3	Ethylmorphine hydrochloride	5.3	Silver protein, mild	5.7
Amobarbital sodium	8.3	Fluorescein sodium	10.3	Sodium acetate	15.3
Amphetamine phosphate	11.3	Glycerin	11.7	Sodium bicarbonate	21.7
Amphetamine sulfate	7.3	Holocaine hydrochloride	6.7	Sodium biphosphate, anhydrous	15.3
Antipyrine	5.7	Homatropine hydrobromide	5.7	Sodium biphosphate	13.3
Apomorphine hydrochloride	4.7	Homatropine methylbromide	6.3	Sodium bisulfite	20.3
Ascorbic acid	6.0	Hyoscyamine sulfate	4.7	Sodium borate	14.0
Atropine methylbromide	4.7	Neomycin sulfate	3.7	Sodium iodide	13.0
Atropine sulfate	4.3	Oxytetracycline hydrochloride	4.3	Sodium metabisulfite	22.3
Bacitracin	1.7	Penicillin G, potassium	6.0	Sodium nitrate	22.7
Barbital sodium	10.0	Penicillin G, sodium	6.0	Sodium phosphate	9.7
Bismuth potassium tartrate	3.0	Pentobarbital sodium	8.3	Sodium propionate	20.3
Boric acid	16.7	Phenobarbital sodium	8.0	Sodium sulfite, exsiccated	21.7
Butacaine sulfate	6.7	Physostigmine salicylate	5.3	Sodium thiosulfate	10.3
Caffeine and sodium benzoate	8.7	Pilocarpine hydrochloride	8.0	Streptomycin sulfate	2.3
Calcium chloride	17.0	Pilocarpine nitrate	7.7	Sulfacetamide sodium	7.7
Calcium chloride (6 H ₂ O)	11.7	Piperocaine hydrochloride	7.0	Sulfadiazine sodium	8.0
Chlorobutanol (hydrated)	8.0	Polymyxin B sulfate	3.0	Sulfamerazine sodium	7.7
Chlortetracycline sulfate	4.3	Potassium chloride	25.3	Sulfapyridine sodium	7.7
Cocaine hydrochloride	5.3	Potassium nitrate	18.7	Sulfathiazole sodium	7.3
Cupric sulfate	6.0	Potassium phosphate, monobasic	14.7	Tetracaine hydrochloride	6.0
Dextrose, anhydrous	6.0	Procainamide hydrochloride	7.3	Tetracycline hydrochloride	4.7
Dibucaine hydrochloride	4.3	Procaine hydrochloride	7.0	Viomycin sulfate	2.7
Dihydrostreptomycin sulfate	2.0	Scopolamine hydrobromide	4.0	Zinc chloride	20.3
Ephedrine hydrochloride	10.0	Scopolamine methylbromide	5.3	Zinc sulfate	5.0
Ephedrine sulfate	7.7	Secobarbital sodium	8.0		
Epinephrine bitartrate	6.0				

^a Table of "Isotonic Solution Values" showing volumes in mL of water to be added to 300 mg of the specified drug in sterile water to produce an isotonic solution. The addition of an isotonic vehicle (commonly referred to as diluting solution) to make 30 mL yields a 1% solution. Solutions prepared as directed above are isoosmotic with 0.9% sodium chloride solution but may not be isotonic with blood (see Appendix A for hemolysis data).

^b V-values for drugs which do not appear in Appendix B, but are listed in Appendix A can be calculated from the sodium chloride equivalent for 1% drug.

Example—Calculate the V-value for anileridine HCl (Appendix A defines E = 0.19).

$$\frac{100 \text{ mL Soln}}{0.9 \text{ g NaCl}} \times \frac{0.19 \text{ g NaCl}}{1 \text{ g drug}} \times 0.3 \text{ g drug} = 6.33 \text{ mL Soln}$$

for dilute solution 6.33 mL soln $\approx$ 6.33 mL water

$$\therefore V = 6.33 \text{ mL water/0.3 g drug}$$

CHAPTER 38

Stability of Pharmaceutical Products

Elizabeth B Vadas, PhD

Senior Director
Pharmaceutical R&D
Merck Frosst Canada, Inc
Point Claire, Dorval
Quebec H9R 4P8
Canada

The use of kinetic and predictive studies for establishing credible expiration dates for pharmaceutical products is now accepted worldwide. However, prior to 1950, only qualitative or semiquantitative methods and procedures were used in pharmaceutical studies. As these rule-of-thumb methods are deficient, they have been replaced by rigorous, scientifically designed studies using reliable, meaningful and specific stability-indicating assays, appropriate statistical concepts and a computer to analyze the resulting data. In this way the maximum amount of valid information is obtained to establish a reliable, defensible expiration date for each formulation.

Stability information is ubiquitous. It may be in a well-planned rigorous kinetic study, in an obscure journal footnote, in a package insert or label copy or in a monograph in a book such as *The Merck Index* or *Physicians' Desk Reference*. Various journals periodically publish digests of compatibility studies. A comprehensive treatment of all aspects of pharmaceutical product stability has been published by Lintner¹ and more recently by Connors, *et al.*²

The main purpose of a quality assurance program is to devise and implement systems and procedures that provide a high probability that each dose or package of a pharmaceutical product will have homogeneous characteristics and properties (within reasonably acceptable limits) to insure both clinical safety and efficacy of the formulation. A broad, well-designed stability-testing plan is an essential and pertinent expansion of the quality assurance program. The assigned expiration date is a direct application and interpretation of the knowledge gained from the stability study.

Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container/closure system, to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications. Assurances that the packaged product will be stable for its anticipated shelf life must come from an accumulation of valid data on the drug in its commercial package. These stability data involve selected parameters which, taken together, form the stability profile.

Stability of a drug also can be defined as the time from the date of manufacture and packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency, and its physical characteristics have not changed appreciably or deleteriously. Although there are exceptions, 90% of labeled potency generally is recognized as the minimum acceptable potency level. Expiration dating then is defined as the time in which the preparation will remain stable when stored under recommended conditions.

An expiration date, which is expressed traditionally in terms of month and year, denotes the last day of the month. The expiration date should appear on the immediate container and the outer retail package. However, when single-dose containers are packaged in individual cartons, the expiration date may be placed on the individual carton instead of the immediate product container. If a dry product is to be reconstituted at the time of dispensing, expiration dates are assigned to both

the dry mixture and the reconstituted product. Tamper-resistant packaging is to be used where applicable.

A second quality assurance goal is drug or clinical safety and it, too, is related closely to pharmaceutical stability. Drug or clinical safety (ie, the nonoccurrence of harm), however, cannot be studied by itself. Rather, it is a negative concept which cannot be proven and must be expressed only in terms of the nonoccurrence of some harmful event. The latter probability, in turn, can be estimated only when the probability occurrence of the harmful event is known.

One type of time-related harmful event is a decrease in therapeutic activity of the preparation to below some arbitrary labeled content. A second type of harmful event is the appearance of a toxic substance, formed as a degradation product upon storage of the formulation. The number of published cases reflecting this second type, fortunately, is few. However, it is possible, though remote, for both types of harmful events to occur simultaneously within the same pharmaceutical product. Thus, the use of stability studies with the resulting application of expiration dating to pharmaceuticals is an attempt to predict the approximate time at which the probability of occurrence of a harmful event may reach an intolerable level. This estimate is subject to the usual Type 1 or alpha error (setting the expiration too early so that the product will be destroyed or recalled from the market at an appreciably earlier time than actually is necessary) and the Type 2 or beta error (setting the date too late so that the harmful event occurs in an unacceptably large proportion of cases). Thus, it is obligatory that the manufacturer clearly and succinctly define the method for determining the degree of change in a formulation and the statistical approach to be used in making the shelf-life prediction. An intrinsic part of the statistical methodology must be the statements of value for the two types of error. For the safety of the patient a Type 1 error can be accepted, but not a Type 2 error.

Requirements

Stability study requirements and expiration dating are covered in the Current Good Manufacturing Practices (GMPs),³ the USP and in the FDA guidelines.⁴

Good Manufacturing Practices—The GMPs³ state that there shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used to determine appropriate storage conditions and expiration dating. The latter is to assure that the pharmaceutical product meets applicable standards of identity, strength, quality and purity at time of use. These regulations, which apply to both human and veterinary drugs, are updated periodically in light of current knowledge and technology.

Compendiums—The compendiums also contain extensive stability and expiration dating information. Included are a discussion of stability considerations in dispensing practices and the responsibilities of both the pharmaceutical manufacturer and the dispensing pharmacist. It now is required that product labeling of official articles provide recommended storage conditions and an expiration date assigned to the specific formulation and package. Official storage conditions are defined as follows: "Cold" is any temperature not exceeding 8°, and "refrigerator" is a cold

place where the temperature is maintained thermostatically between 2° and 8°. A "freezer" is a cold place maintained between -20° and -10°. "Cool" is defined as any temperature between 8° and 15°, and "room temperature" is that temperature prevailing in a working area. "Controlled room temperature" is that temperature maintained thermostatically between 15° and 30°. "Warm" is any temperature between 30° and 40°, while "excessive heat" is any heat above 40°. Should freezing subject a product to a loss of potency or to destructive alteration of the dosage form, the container label should bear appropriate instructions to protect the product from freezing. Bulk packages are exempt from storage requirements if the products are intended for manufacture or repacking for dispensing or distribution. Where no specific storage instructions are given in a monograph, it is understood that the product's storage conditions shall include protection from moisture, freezing and excessive heat.

As is noted above in USP XXII, the definition of controlled room temperature was a "temperature maintained thermostatically between 15° and 30° (59° and 86°F)." This definition invited many interpretations, including storage at any temperature between 15° and 30°, requiring knowledge of stability behavior at each temperature chosen. In an attempt to be more specific and scientifically definitive and to harmonize with international drug standards efforts, the concept of controlled room temperature was given a more exact definition in the Ninth Supplement to USP XXII. The usual or customary temperature range was identified as 20°–25°, with the possibility of encountering excursions in the 15°–30° range and with the introduction of a new concept, the mean kinetic temperature (MKT).

During storage of a pharmaceutical article, degradation takes place at a rate determined by the concentration of the material and the specific rate constant for the degradation process. Since the rate constants are temperature-dependent, the amount of degradation varies as temperature changes during a storage period. In order to determine the total amount of thermal degradation, it is necessary to calculate individual losses at each temperature and sum them. In an attempt to simplify this determination, the MKT has been used. The MKT is the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures. Thus, the MKT may be considered as an isothermal storage temperature that simulates the non-isothermal effects of storage temperature variations.

FDA Guidelines provide recommendations for—

1. The design of stability studies to establish appropriate expiration dating periods and product storage requirements.
2. The submission of stability information for investigational new drugs, biologicals, new drug applications and biological product license applications.

Thus, the guidelines represent a framework for the experimental design and data analysis as well as the type of documentation needed to meet regulatory requirements in the drug-development process.

The above framework, however, has been re-evaluated and revised significantly in the last few years with the aim of harmonizing the technical requirements for the registration of pharmaceuticals worldwide. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a unique project which brought together regulatory authorities and experts from the pharmaceutical industry from three regions of the world; Europe, Japan and the US. The first conference (ICH1) took place in November 1991 in Brussels and the second conference (ICH2) in Orlando, FL in October 1993. These conferences provided an open forum for discussion and resulted in the creation of an extensive set of guidelines dealing with the many aspects of safety, quality and efficacy of medicinal products. The ICH Harmonized Tripartite Guideline provides a general indication on the requirements for "Stability Testing of New Drug Substances and Products." The main thrust of the stability guideline centers around criteria for setting up stability protocols shown in Table 1.

The guidelines have been published in a draft form in the *Federal Register*, April 16, 1993. Publication of the final guidelines is expected in 1994 with implementation of the guidelines occurring with Registration Applications after January 1, 1998.

Product Stability

Many factors affect the stability of a pharmaceutical product, including the stability of the active ingredient(s), the potential interaction between active and inactive ingredients,

Table 1

	Conditions	Minimum time period at submission
Long-term testing	25°C ± 2°C/60% RH ± 5%	12 mo
Accelerated testing	40°C ± 2°C/75% RH ± 6%	6 mo
Alternate testing ^a	30°C ± 2°C/60% RH ± 5%	

^aRequired if "significant change" occurs during 6-mo storage under conditions of accelerated testing.

the manufacturing process, the dosage form, the container-liner-closure system and the environmental conditions encountered during shipment, storage, handling and length of time between manufacture and usage.

Classically, pharmaceutical product stability evaluations have been separated into studies of chemical (including biochemical) and physical stability of formulations. Realistically, there is no absolute division between these two arbitrary divisions. Physical factors—such as heat, light and moisture—may initiate or accelerate chemical reactions, while every time a measurement is made on a chemical compound, physical dimensions are included in the study.

In this treatment, physical and chemical stability will be discussed along with those dosage form properties which can be measured and are useful in predicting shelf life. The effect of various physical and chemical phenomena of pharmaceuticals also will be treated.

Knowledge of the physical stability of a formulation is very important for three primary reasons. First, a pharmaceutical product must appear fresh, elegant and professional, so long as it remains on the shelf. Any changes in physical appearance such as color fading or haziness can cause the patient or consumer to lose confidence in the product. Second, since some products are dispensed in multiple-dose containers, uniformity of dose content of the active ingredient over time must be assured. A cloudy solution or a broken emulsion can lead to a nonuniform dosage pattern. Third, the active ingredient must be available to the patient throughout the expected shelf life of the preparation. A breakdown in the physical system can lead to nonavailability of the medicament to the patient. In the case of metered-dose inhaler pulmonary aerosols, particle aggregation may result in inadequate lung deposition of the medication.

The chemical causes of drug deterioration have been classified into incompatibility, oxidation, reduction, hydrolysis, racemization and others. In the latter category, decarboxylation, deterioration of hydrogen peroxide and hypochlorites and the formation of precipitates have been included.

Galenical Dosage Forms

As the various galenical dosage forms present unique stability problems, they will be discussed separately in the following section.

Suspensions—A stable suspension can be redispersed homogeneously with moderate shaking and easily can be poured throughout its shelf life, with neither the particle-size distribution, the crystal form or the physiological availability of the suspended active ingredient changing appreciably with time.

Most stable pharmaceutical suspensions are flocculated; that is, the suspended particles are bonded together physically to form a loose, semirigid structure. The particles are said to uphold each other while exerting no significant force on the liquid. Sedimented particles of a flocculated suspension can be redispersed easily at any time with only moderate shaking.

In nonflocculated suspensions, the particles remain as individuals unaffected by neighboring particles and are affected only by the suspension vehicle. These particles, which are smaller and lighter, settle slowly, but once they have settled, often form a rock-hard, difficult-to-disperse sediment. Non-flocculated suspensions can be made acceptable by decreas-

ing the particle size of the suspended material or by increasing the density and viscosity of the vehicle, thus reducing the possibility of settling.

When studying the stability of a suspension, first determine with a differential manometer if the suspension is flocculated. If the suspension is flocculated, the liquid will travel the same distance in the two side arms. With nonflocculated suspensions, the hydrostatic pressures in the two arms are unequal; hence, the liquids will be at different levels.

The history of settling of the particles of a suspension may be followed by a Brookfield viscometer fitted with a Helipath attachment. This instrument consists of a rotating T-bar spindle which descends slowly into the suspension as it rotates. The dial reading on the viscometer is a measure of the resistance that the spindle encounters at various levels of the sedimented suspension. This test must be run only on fresh, undisturbed samples (see Chapter 22).

An electronic particle counter and sizer, such as a Coulter counter, or a microscope may be used to determine changes in particle-size distribution. Crystal form alterations may be detected by a microscopic examination and, when suspected, must be confirmed by X-ray powder diffraction.

All suspensions should be subjected to cycling temperature conditions to determine the tendency for crystal growth to occur within a suspension. Shipping tests, ie, transporting bottles across the country by rail or truck, also are used advantageously to study the stability of suspensions.

Emulsions—A stable emulsion can be redispersed homogeneously to its original state with moderate shaking and can be poured at any stage of its shelf life. Although most of the important pharmaceutical emulsions are of the O/W type, many stability test methods can be applied to either an O/W or a W/O emulsion.

Two simple tests are used to screen emulsion formulations. First, the stability of an emulsion can be determined by heating it to 50 to 70° and its gross physical stability observed visually or checked by turbidimetric measurements. Usually the emulsion that is the most stable to heat is the one most stable at room temperature. However, this may not be true always because an emulsion at 60° may not be the same as it is at room temperature. Second, the stability of the emulsion can be estimated by the "coalescence time" test. Although this is only a rough quantitative test, it is useful for detecting gross differences in emulsion stability at room temperature.

Emulsions also should be subjected to refrigeration temperatures. An emulsion stable at room temperature has been found to be unstable at 4°. It was reasoned that an oil-soluble emulsifier precipitated at the lower temperature and disrupted the system. An emulsion chilled to the extent that the aqueous base crystallizes is damaged irreversibly.

The ultracentrifuge also is used to determine emulsion stability. When the amount of separated oil is plotted against the time of centrifugation, a plateau curve is obtained. A linear graph results when the oil flotation (creaming) rate is plotted vs the square of the number of centrifuge revolutions per minute. The flotation rate is represented by the slope of the line resulting when the log distance of emulsion-water boundary from the rotor center is plotted against time for each revolution per minute.

For stability studies, two batches of an emulsion should be made at one time on two different sizes of equipment. One should be a bench-size lot and the other a larger, preferably production-size, batch. Different types of homogenizers produce different results and different sizes of the same kind of homogenizer can yield emulsions with different characteristics.

Solutions—A stable solution retains its original clarity, color and odor throughout its shelf life. Retention of clarity of a solution is a main concern of a physical stability program. As visual observation alone under ordinary light is a poor test of clarity, a microscope light should be projected through a diaphragm into the solution. Undissolved particles will scatter the light and the solution will appear hazy. While the

Coulter counter also can be used, light-scattering instruments are the most sensitive means of following solution clarity.

Solutions should remain clear over a relatively wide temperature range such as 4 to 47°. At the lower range an ingredient may precipitate due to its lower solubility at that temperature, while at the higher temperature homogeneity may be destroyed by the flaking of particles from the glass containers or rubber closures. Thus, solutions should be subjected to cycling temperature conditions.

The stability program for solutions also should include a study of pH changes, especially when the active ingredients are soluble salts of insoluble acids or bases. Among other tests are observations for changes in odor, appearance, color, taste, light-stability, redispersibility, suspendibility, pourability, viscosity, isotonicity, gas evolution, microbial stability, specific gravity, surface tension and pyrogen content in the case of parenteral products.

When solutions are filtered, the filter medium may absorb some of the ingredients from the solution. Thus, the same type of filter should be used for preparing the stability samples as will be used to prepare the production-size batches.

For dry-packaged formulations, intended to be reconstituted prior to use, the visual appearance should be observed on both the original dry material and on the reconstituted preparation. The color and odor of the cake, the color and odor of the solution, the moisture content of the cake and the rate of reconstitution should be followed as a part of its stability profile.

Tablets—Stable tablets retain their original size, shape, weight and color under normal handling and storage conditions throughout their shelf life. In addition, the *in vitro* availability of the active ingredients should not change appreciably with time.

Excessive powder or solid particles at the bottom of the container, cracks or chips on the face of a tablet or appearance of crystals on the surface of tablets or on container walls are indications of physical instability of uncoated tablets. Hence, the effect of mild, uniform and reproducible shaking and tumbling of tablets should be studied. After visual observation of the tablets for chips, cracks and splits, the intact tablets are sorted and weighed to determine the amount of material worn away by abrasion. The results of these tests are comparative rather than absolute and should be correlated with actual stress experience. Packaged tablets also should be subjected to cross-country shipping tests as well as to various "drop tests."

Tablet hardness (or resistance to crushing or fracturing) can be followed by the commercially available hardness testers. As results will vary with the specific make of the test apparatus used, direct comparison of results obtained on different instruments cannot be made. Thus, the same instrument should be used consistently throughout a particular study.

Color stability of tablets can be followed by an appropriate colorimeter or reflectometer with heat, sunlight and intense artificial light employed to accelerate the color deterioration. Caution must be used in interpreting the elevated temperature data as the system at that temperature may be different from that at a lower temperature. It is not always proper to assume that the same changes will occur at elevated temperatures as will be evidenced later at room temperature. Evidence of instability of coated tablets also is indicated by cracks, mottling or tackiness of the coating.

For the more insoluble tableted active ingredients, the results of dissolution tests are more meaningful than disintegration results for making bioavailability predictions. Dissolution rate tests should be run in an appropriate medium such as artificial gastric and/or intestinal juice at 37° (see Chapter 34). When no significant change (such as a change in the polymorphic form of the crystal) has occurred, an unaltered dissolution-rate profile of a tablet formulation usually indicates constant *in vivo* availability.

Disintegration tests may be used to detect periodic gross changes in the physical characteristics of a tablet, but these tests must be correlated with the dissolution-rate study of a

particular tableted product. When there is no such correlation, *in vivo* tests must be run. The release pattern of sustained-release formulations should be determined periodically during the stability test period.

Uniformity of weight, odor, texture, drug and moisture contents and humidity effect also are studied during a tablet stability test.

Gelatin Capsules—When stored under adverse conditions, capsule shells may soften and stick together or harden and crack under slight pressure. They should be protected from sources of microbial contamination. The shell of soft gelatin capsules should contain a preservative to prevent the growth of fungi. Encapsulated products, like all other dosage forms, must be packaged properly.

Ointments—Ointments have been defined as high-viscosity suspensions of active ingredients in a nonreacting vehicle. A stable ointment is one which retains its homogeneity throughout its shelf-life period. The main stability problems seen in ointments are "bleeding" and changes in consistency due to aging or changes in temperature. When fluid components such as mineral oil separate at the top of an ointment, the phenomenon is known as "bleeding" and can be observed visually. Unfortunately, as there is no known way to accelerate this event, the tendency to "bleed" cannot be predicted.

An ointment which is too soft is messy to use while one which is very stiff is difficult to extrude and apply. Hence, it is important to be able to define quantitatively the consistency of an ointment. This may be done with a penetrometer, an apparatus which allows a pointed weight to penetrate into the sample under a measurable force. The depth of the penetration is a measure of the consistency of an ointment. Consistency also can be measured by the Helipath attachment to a high-viscosity viscometer or by a Burrell Severs rheometer. In the latter instrument the ointment is loaded into a cylinder and extruded with a measured force. The amount extruded is a measure of the consistency of the ointment.

Ointments have a considerable degree of structure which requires a minimum of 48 hours to develop after preparation. As rheological data on a freshly made ointment may be erroneous, such tests should be performed only after the ointment has achieved equilibrium.

Slight changes in temperature (1 or 2°) can affect the consistency of an ointment greatly; hence, rheological studies on ointments must be performed only at constant and controlled temperatures.

Among the other tests performed during the stability study of an ointment are a check of visual appearance, color, odor, viscosity, softening range, consistency, homogeneity, particle-size distribution and sterility.

Undissolved components of an ointment may change in crystal form or in size with time. Microscopic examination or an X-ray diffraction measurement may be used to monitor these parameters.

In some instances it is necessary to use an ointment base that is less than ideal in order to achieve the required stability. For example, drugs that hydrolyze rapidly are more stable in a hydrocarbon base than in a base containing water, even though they may be more effective in the latter.

Incompatibility

Obvious sources of pharmaceutical instability include the incompatibility of various ingredients within a formulation. Numerous examples are described in other sections of this book and the literature is replete with illustrations. Thus, the subject need not be treated in detail here.

While undesirable reactions between two or more drugs are said to result in a "physical," "chemical" or "therapeutic" incompatibility, physical incompatibility is somewhat of a misnomer. It has been defined as a physical or chemical interaction between two or more ingredients which leads to a visibly recognizable change. The latter may be in the form of a gross precipitate, haze or color change.

On the other hand, a chemical incompatibility is classified

as a reaction in which a visible change does not occur. Since there is no visible evidence of deterioration, this type of incompatibility requires trained, knowledgeable personnel to recognize it, should it occur.

A therapeutic incompatibility has been defined as an undesirable pharmacological interaction between two or more ingredients which leads to (1) potentiation of the therapeutic effects of the ingredients, (2) destruction of the effectiveness of one or more of the ingredients or (3) occurrence of a toxic manifestation within the patient.

Oxidation-Reduction

Oxidation is a prime cause of product instability and often, but not always, the addition of oxygen or the removal of hydrogen is involved. When molecular oxygen is involved, the reaction is known as auto-oxidation because it occurs spontaneously, though slowly, at room temperature.

Oxidation, or the loss of electrons from an atom, frequently involves free radicals and subsequent chain reactions. Only a very small amount of oxygen is required to initiate a chain reaction. In practice, it is easy to remove most of the oxygen from a container, but very difficult to remove it all. Hence, nitrogen and carbon dioxide frequently are used to displace the headspace air in pharmaceutical containers to help minimize deterioration by oxidation.

As an oxidation reaction is complicated, it is difficult to perform a kinetic study on oxidative processes within a general stability program. The redox potential, which is constant and relatively easy to determine, can, however, provide valuable predictive information. In many oxidative reactions, the rate is proportional to the concentration of the oxidizing species but may be independent of the concentration of the oxygen present. The rate is influenced by temperature, radiation and the presence of a catalyst. An increase in temperature leads to an acceleration in the rate of oxidation. If the storage temperature of a preparation can be reduced to 0 to 5°, usually it can be assumed that the rate of oxidation will be at least halved.

Trace amounts of heavy metals such as cupric, chromic, ferrous or ferric ions may catalyze oxidation reactions. As little as 0.2 mg of copper ion per liter considerably reduces the stability of penicillin. Similar examples include the deterioration of epinephrine, phenylephrine, lincomycin, isoprenaline and procaine hydrochloride. Adding chelating agents to water to sequester heavy metals and working in special manufacturing equipment (eg, glass) are some means used to reduce the influence of heavy metals on a formulation. Parenteral formulations should not come in contact with heavy metal ions during their manufacture, packaging or storage.

Hydronium and hydroxyl ions catalyze oxidative reactions. The rate of decomposition for epinephrine, for example, is more rapid in a neutral or alkaline solution with maximum stability (minimum oxidative decomposition) at pH 3.4. There is a pH range for maximum stability for any antibiotic and vitamin preparation which usually can be achieved by adding an acid, alkali or buffer.

Oxidation may be inhibited by the use of antioxidants, called negative catalysts. They are very effective in stabilizing pharmaceutical products undergoing a free-radical-mediated chain reaction. These substances, which are easily oxidizable, act by possessing lower oxidation potentials than the active ingredient. Thus, they undergo preferential degradation or act as chain inhibitors of free radicals by providing an electron and receiving the excess energy possessed by the activated molecule.

The ideal antioxidant should be stable and effective over a wide pH range, soluble in its oxidized form, colorless, non-toxic, nonvolatile, nonirritating, effective in low concentrations, thermostable and compatible with the container-closure system and formulation ingredients.

The commonly used antioxidants for aqueous systems include sodium sulfite, sodium metabisulfite, sodium bisulfite, sodium thiosulfate and ascorbic acid. For oil systems, ascor-

byl palmitate, hydroquinone, propyl gallate, nordihydroguaiaretic acid, butylated hydroxytoluene, butylated hydroxyanisole and alpha-tocopherol are employed.

Synergists, which increase the activity of antioxidants, are generally organic compounds that complex small amounts of heavy metal ions (see Chapter 14). These include the ethylenediamine tetraacetic acid (EDTA) derivatives, dihydroethylglycine, citric, tartaric, gluconic and saccharic acids. EDTA has been used to stabilize ascorbic acid, oxytetracycline, penicillin, epinephrine and prednisolone.

Reduction reactions are much less common than oxidative processes in pharmaceutical practice. Examples include the reduction of gold, silver or mercury salts by light to form the corresponding free metal.

Hydrolysis

Drugs containing an ester or amide linkage are prone to hydrolysis. Some examples include cocaine, physostigmine, procaine, tetracaine, thiamine and benzylpenicillin.

The rate of hydrolysis depends on the temperature and the pH of the solution. A much quoted rule-of-thumb is that for each 10° rise in storage temperature, the rate of reaction doubles or triples. As this is an empiricism, it is not applicable always.

When hydrolysis occurs, the concentration of the active ingredient decreases while the concentration of the decomposition products increases. The effect of this change on the rate of the reaction depends on the order of the reaction. With zero-order reactions the rate of decomposition is independent of concentration of the ingredient. Although weak solutions decompose at the same absolute rate as stronger ones, the weaker the solution, the greater the proportion of active ingredient destroyed in a given time; ie, the percentage of decomposition is greater in weaker solutions. Increasing the concentration of an active ingredient which is hydrolyzing by zero-order kinetics will slow the percentage decomposition.

With first-order reactions, which occur frequently in the hydrolysis of drugs, the rate of change is directly proportional to the concentration of the reactive substance. Thus, changes in the concentration of the active ingredient have no influence on the percentage decomposition.

As many hydrolytic reactions are catalyzed by both hydronium and hydroxyl ions, pH is an important factor in determining the rate of a reaction. The pH range of minimum decomposition (or maximum stability) depends on the ion having the greatest effect on the reaction. If the minimum occurs at about pH 7, the two ions are of equal effect. A shift of the minimum toward the acid side indicates that the hydroxyl ion has the stronger catalytic effect and *vice versa* in the case of a shift toward the alkaline side. In general, hydroxyl ions have the stronger effect. Thus, the minimum is often found between pH 3 and 4.

Sometimes, it is necessary to compromise between the optimum pH for stability and that for pharmacological activity. For example, several local anesthetics are most stable at a distinctly acid pH, whereas for maximum activity they should be neutral or slightly alkaline.

Small amounts of acids, alkalies or buffers are used to adjust the pH of a formulation. Buffers are used when small changes in pH are likely to cause major degradation of the active ingredient.

Obviously, the amount of water present can have profound effect on the rate of a hydrolysis reaction. When the reaction takes place fairly rapidly in water, other solvents sometimes can be substituted. For example, barbiturates are much more stable at room temperature in propylene glycol-water than in water alone.

Modification of chemical structure may be used to retard hydrolysis. In general, as it is only the fraction of the drug in solution that hydrolyzes, a compound may be stabilized by reducing its solubility. This can be done by adding various substituents to the alkyl or acyl chain of aliphatic or aromatic esters or to the ring of an aromatic ester. In some cases

less-soluble salts or esters of the parent compound have been found to aid product stability. Steric and polar complexation also have been employed to alter the rate of hydrolysis. Caffeine complexes with local anesthetics such as benzocaine, procaine or tetracaine to reduce the rate of hydrolysis and thus promote stability.

Surfactants also may be used to stabilize drugs. For example, the half-life of benzocaine was increased 18 times by the addition of sodium lauryl sulfate.

Decarboxylation

Pyrolytic solid-state degradation through decarboxylation usually is not encountered in pharmacy, as relatively high heats of activation (25 to 30 kcal) are required for the reaction. However, solid *p*-aminosalicylic acid undergoes pyrolytic degradation to *m*-aminophenol and carbon dioxide. The reaction, which follows first-order kinetics, is highly pH-dependent and is catalyzed by hydronium ions. The decarboxylation of *p*-aminobenzoic acid occurs only at extremely low pH values and at high temperatures.

Racemization

Racemization or the action or process of changing from an optically active compound into a racemic compound or an optically inactive mixture of corresponding dextro (*d*-) and levo (*l*-) forms is a major factor in pharmaceutical stability. Frequently, the *l*-form is more pharmacologically active than the *d*-form. For example, *l*-epinephrine is 15 to 20 times more active than its *d*-counterpart, while the activity of the racemic mixture is just over one-half that of the *l*-form. Current nomenclature practice uses (+) for *d*- and (−) for *l*-, therefore, *l*-epinephrine would be named (−)-epinephrine, etc. Refer to Chapter 24 for a more detailed treatment.

In general, racemization follows first-order kinetics and depends on temperature, solvent, catalyst and the presence or absence of light. Racemization appears to depend on the functional group bound to the asymmetric carbon atom, with aromatic groups tending to accelerate the process.

Photochemical

Photolytic degradation can be an important limiting factor in the stability of pharmaceuticals.

A drug can be affected chemically by radiation of a particular wavelength only if it absorbs radiation at that wavelength and the energy exceeds a threshold. Ultraviolet radiation, which has a high energy level, is the cause of many degradation reactions.

If the absorbing molecule reacts, the reaction is said to be photochemical in nature. Where the absorbing molecules do not participate directly in the reaction, but pass their energy to other reacting molecules, the absorbing substance is said to be a photosensitizer.

As many variables may be involved in a photochemical reaction, the kinetics can be quite complex. The intensity and wavelength of the light and the size, shape, composition and color of the container may affect the velocity of the reaction.

The photodegradation of chlorpromazine through a semiquinone free-radical intermediate follows zero-order kinetics. On the other hand, alcoholic solutions of hydrocortisone, prednisolone and methylprednisolone degrade by reactions following first-order kinetics.

Colored-glass containers most commonly are used to protect light-sensitive formulations. Yellow-green glass gives the best protection in the ultraviolet region, while amber confers considerable protection from ultraviolet radiation but little from infrared. Riboflavin is best protected by a stabilizer which has a hydroxyl group attached to or near the aromatic ring. The photodegradation of sulfacetamide solutions may be inhibited by an antioxidant such as sodium thiosulfate or metabisulfite.

Ultrasonic Energy

Ultrasonic energy, which consists of vibrations and waves with frequencies greater than 20,000 Hz, promotes the formation of free radicals and alters drug molecules.

Changes in prednisolone, prednisone acetate or deoxycorticosterone acetate suspensions in an ultrasonic field have been observed spectrometrically in the side chain at C-17 and in the oxo group of the A ring. With sodium alginate, in an ultrasonic field, it has been reported that above a minimum power output, degradation increased linearly with increased power.

Ionizing Radiation

Ionizing radiation, particularly gamma rays, has been used for the sterilization of certain pharmaceutical products. At the usual sterilizing dose, 2.5 mRad, it seldom causes appreciable chemical degradation. In general, formulations which are in the solid or frozen state are more resistant to degradation from ionizing radiation than those in liquid form. For example, many of the vitamins are little affected by irradiation in the solid state, but are decomposed appreciably in solution. On the other hand, both the liquid- and solid-state forms of atropine sulfate are affected seriously by radiation.

Predicting Shelf Life

The technique of estimating the shelf life of a formulation from its accumulated stability data has evolved from examining the data and making an educated guess through plotting the time-temperature points on appropriate graph paper and crudely extrapolating a regression line to the application of rigorous physical-chemical laws, statistical concepts and computers to obtain meaningful, reliable estimates.

A simple means of estimating shelf life from a set of computer-prepared tables has been described by Lintner *et al.*⁵ This system was developed to select the best prototype formulation based on short-term stability data and predict both estimated and minimum shelf-life values for the formulation. It is a middle-ground approach between the empirical methods and the modern, rigorous statistical concepts. All calculations can be made readily by hand and the estimated values can be obtained easily from appropriate tables. The system assumes that

1. Shelf-life predictions can be made satisfactorily for lower temperatures using the classical Arrhenius model from data obtained at higher temperatures.
2. The energy of activation of the degradation reaction is between 10 to 20 kcal/mole (this is a safe assumption, as Kennon⁶ has noted, that rarely are drugs with energies of activation of less than 10 kcal/mole used in pharmacy and, for values as high as 20 kcal/mole, the error in the shelf-life prediction will be on the conservative side).
3. The rate of decomposition will not increase beyond that already observed.
4. The standard deviation of the replicated assays is known, or can be estimated from the analytical data.

This concept further assumes that the degradation reaction follows zero- or pseudo-zero-order kinetics. As shown in Fig. 1, this is an excellent assumption. For data corresponding to a zero-, first- or second-order degradation pattern, it is impossible to distinguish one order from another with usual analytical procedures, where the total degraded material is not large. In addition, shelf-life calculations assuming zero-order kinetics are more conservative than those for higher orders.

This middle-ground system is useful in creating the experimental design for the stability study. The formulator has the opportunity to study various combinations of parameters to try to optimize the physical-statistical model. One can check the effect of improving the assay standard deviation, running additional replicates, using different time points and assuming various degradation rates and energies of activation on the stability of the test formulation.

McMinn and Lintner later developed and reported on an

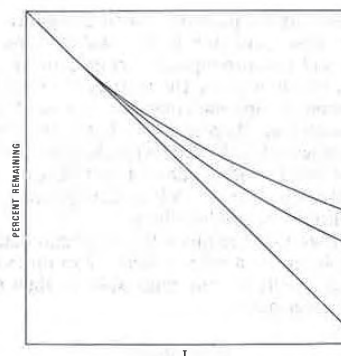


Fig. 1. Zero-order plots for reactions which are zero-, first- and second-order.

information-processing system for handling product stability data.⁷ This system saves the time of formulators in analyzing and interpreting their product stability data, in addition to minimizing the amount of clerical help needed to handle an ever-increasing assay load. For products, such as those of vitamins for example, where large overages are required, the statistical portions of this advanced technique aid the manufacturer to tailor the formula composition to obtain the desired and most economical expiration dating.

This system stores both physical and chemical data and retrieves the information in three different formats (one of which was designed specifically for submitting to regulatory agencies). It analyzes single-temperature data statistically by analysis of covariance and regression or multiple-temperature data by weighted or unweighted analysis using the Arrhenius relationship; provides estimates of the shelf life of the preparation with the appropriate confidence intervals; preprints the assay request cards which are used to record the results of the respective assay procedures and to enter the data into the system and produces a 5-year master-stability schedule as well as periodic 14-day schedules of upcoming assays.

As mentioned above, a portion of the advanced system analyzes the stability data obtained at a single temperature by analysis of covariance and regression. This analysis is based on the linear (zero-order) model

$$Y_{ij} = \beta_i X_{ij} + \alpha_i + \epsilon_{ij} \quad (1)$$

where Y_{ij} is the percent of label of the j th stability assay of the i th lot, X_{ij} is the time in months at which Y_{ij} was observed, β_i and α_i are the slope and intercept respectively of the regression line of the i th lot and ϵ_{ij} is a random error associated with Y_{ij} . The random errors are assumed to be identically and independently distributed normal variables with a zero mean and a common variance, σ^2 .

A summary of the regression analysis for each individual lot, and for the combination of these lots, plus a summary of the analyses of covariance and deviation from regression are prepared by the computer.

Because the computer combines, or pools, the stability data from the individual lots, irrespective of the statistical integrity of this step, the pooled data are examined for validity by the F test. The mean square of the regression coefficient (slope) is divided by the mean square of the deviation within lots, and similarly, the adjusted mean (y intercept) is divided by the common mean square to give the respective F ratios. The latter values then are compared to the critical 5% F values. When the calculated F values are smaller than the critical F values, the data may be combined and the pooled data analyzed.

A printout for the combined lots as well as for each individual lot provides the estimated rate of degradation and its standard error in percent per month for each ingredient. The

student t value is calculated from these estimates and tested for significance from zero. When the *t* value is significant, the printout contains an estimate of the shelf life with the appropriate confidence interval. When the *t* value is not significantly different from zero, estimates of the minimum and projected shelf-life values are made. In addition, coordinates of the calculated least-squares regression line with appropriate confidence limits for the mean and individual predicted assays are printed.

Plots of the resulting least-squares line containing the individual data points also are printed by the computer. For the calculation of X_0 , $\hat{Y}$ equals $\bar{Y} + \hat{\beta}(X_0 - \bar{X})$ where $\hat{\beta}$ is the least-squares estimate of the slope and $\bar{X}$ is the mean time of assay.

The sample variance for this estimate, $S^2(\hat{Y})$, is equal to

$$S_{\hat{Y}}^2 = \left[\frac{1}{N} + \frac{(X_0 - \bar{X})^2}{\sum (X_{ij} - \bar{X})^2} \right] \quad (2)$$

where N is the number of assays. The 95% confidence interval is equal to $\hat{Y} \pm t_{0.05S}(\hat{Y})$.

For cases where the slope of the best fitting line is positive and significantly different from zero (resulting, for example, from solvent evaporation), the statement "no degradation has been detected and hence no shelf-life estimate is made" is printed. Where the computed line has a positive slope but not significantly different from zero, only the minimum shelf-life value is calculated.

Traditionally, extensive stability data are collected at the recommended storage temperatures (usually refrigerator and/or room temperature) to be placed on the label of the package. However, elevated-temperature data are very valuable in determining the shelf life of a product. In practice, multiple levels of thermal stress are applied to the formulation so that appropriate shelf-life estimates can be made for normally expected marketing conditions. In cases where data from accelerated studies are used to project a tentative expiration date that is beyond the date supported by actual shelf-life studies, testing must continue until the tentative expiration date is verified.

It was noted in Chapter 18 that the effect of temperature variation on the rate of a reaction can be expressed by an integrated form of the Arrhenius equation

$$k = se^{-E_A/RT} \quad (3)$$

$$\log \frac{k_2}{k_1} = \frac{E_A}{2.303R} \left(\frac{T_2 - T_1}{T_2 \cdot T_1} \right) \quad (4)$$

A weighted modification of this model has been incorporated into the previously described computerized system. Each printout contains a statement concerning the acceptability of the Arrhenius assumption with its appropriate probability level, the slope and intercept for the Arrhenius line, the estimated apparent energy of activation with its 95% confidence limits plus the estimated shelf-life values at selected temperatures.

The analysis of first-order stability data is based on the linear model

$$Y_{ij} = \alpha_i + \beta_i X_{ij} + \epsilon_{ij} \quad (5)$$

where Y_{ij} is the natural logarithm of the assay value for the j th observation of the i th temperature, X_{ij} is the elapsed time in months for the assay sample for the i th temperature, β_i and α_i are the slope and intercept respectively and ϵ_{ij} is a random error associated with Y_{ij} . The errors are assumed to be distributed identically and independently, normally with a zero mean and variance σ^2 .

For orders other than first, Y_{ij} represents the concentration raised to the power of 1 minus the order.

The estimated rate constant (ie, the negative slope) is

$$-b_i = - \sum_j (Y_{ij} - Y_i)(X_{ij} - X_i) / \sum_j (X_{ij} - X_i)^2 \quad (6)$$

The standard error of the estimated rate constant is

$$S_{-b_i} = \frac{S(Y/X)}{[\sum (X_{ij} - X_i)^2]^{1/2}} \quad (7)$$

where $S(Y/X)$, the residual standard error, is equal to

$$S(Y/X) = \left\{ \frac{1}{N-2} \left[\sum_{j=1}^{12} (Y_{ij} - Y_i)^2 - \frac{[\sum (X_{ij} - X_i)(Y_{ij} - Y_i)]^2}{\sum (X_{ij} - X_i)^2} \right] \right\}^{1/2} \quad (8)$$

According to the Arrhenius relationship, faster degradation occurs at the higher temperatures; hence, assays for the high-temperature data usually are run more often but for a shorter period of time. The effect of simple least-squares analysis of this type of data is to force the Arrhenius equation through the low temperature data and essentially ignore the high-temperature information. Thus, much more credence is placed in the point estimates of the low temperature than is warranted. In addition, the usual confidence limits on extrapolated degradation rates at refrigerator or room temperature cannot be made validly. For these reasons, Bentley⁸ presented a method based on a weighted least-squares analysis to replace the unweighted approximation. He also developed a statistical test for the validity of the Arrhenius assumption which is computed easily from the results of the unweighted method.

To make shelf-life estimates from elevated temperature data, two storage temperatures are obviously the minimum. As the accuracy of the extrapolation is enhanced by using additional temperatures, a minimum of four different temperatures is recommended for most product stability studies. With the current use of computers to do the bulk of stability calculations, including weighted least-squares analysis, the temperatures and storage conditions need not be selected for arithmetic convenience.

It is not necessary to determine the mechanism of the degradation reaction. In most cases, it is necessary only to follow some property of degradation and to linearize this function. Either the amount of intact drug or the amount of a formed degradation product may be followed. It usually is impractical to determine the exact order of the reaction. With assay errors in the range of 2 to 5%, at least 50% decomposition must occur before the reaction order can be determined. As the loss with pharmaceuticals generally is less, zero-order kinetics should be assumed, unless the reaction order is known from previous work. In any case, replication of stability assays is advisable.

The batches of drugs used for a stability study should be representative of production run material or at least of a known degree of purity. The quality of the excipients also should be known as their impurities, or even their moisture content, can affect product stability deleteriously. Likewise, the samples of the formulation taken for the stability study must be representative of the lot.

Specific, stability-indicating assay methods must be used in order to make meaningful shelf-life estimates. The reliability and specificity of the test method on the intact molecule and on the degradation products must be demonstrated.

Addition of Overage

The problem of declining potency, in an unstable preparation, can be ameliorated by the addition of an excess or overage of the active ingredient. Overages, then, are added to pharmaceutical formulations to keep the content of the active ingredient within the limits compatible with therapeutic requirements, for a predetermined period of time.

The amount of the overage depends upon the specific ingredient and the galenical dosage form. The International Pharmaceutical Federation has recommended that overages be limited to a maximum of 30% over the labeled potency of an ingredient.

Pharmaceutical Containers

Unless otherwise indicated in a compendial monograph, the official standards for containers apply to articles packaged either by the pharmaceutical manufacturer or the dispensing pharmacist. In general, repackaging of pharmaceuticals is inadvisable. However, if repackaging is necessary, the manufacturer of the product should be consulted for potential stability problems.

A pharmaceutical container has been defined as a device which holds the drug and is, or may be, in direct contact with the preparation. The immediate container is described as that which is in direct contact with the drug at all times. The liner and closure traditionally have been considered to be part of the container system. The container should not interact physically or chemically with the formulation so as to alter the strength, quality or purity of its contents beyond permissible limits.

The choice of containers and closures can have a profound effect on the stability of many pharmaceuticals. Now that a large variety of glass, plastics, rubber closures, tubes, tube liners, etc are available, the possibilities for interaction between the packaging components and the formulation ingredients are immense. Some of the packaging elements themselves are subject to physical and chemical changes that may be time-temperature dependent.

Frequently, it is necessary to use a well-closed or a tight container to protect a pharmaceutical product. A *well-closed container* is used to protect the contents from extraneous solids or a loss in potency of the active ingredient under normal commercial conditions. A *tight container* protects the contents from contamination by extraneous materials, loss of contents, efflorescence, deliquescence or evaporation and is capable of tight reclosure. When the packaging and storage of an official article in a well-closed or tight container is specified, water-permeation tests should be performed on the selected container.

In a stability program, the appearance of the container with special emphasis on the inner walls, the migration of ingredients onto/into the plastic or into the rubber closure, the migration of plasticizer or components from the rubber closure into the formulation, the possibility of two-way moisture penetration through the container walls, the integrity of the tac-seal and the back-off torque of the cap must be studied.

Glass, plastics and/or metals are the commonly used components of pharmaceutical containers.

Traditionally, glass has been the most widely used container for pharmaceutical products to insure inertness, visibility, strength, rigidity, moisture protection, ease of reclosure and economy of packaging. While glass has some disadvantages, such as the leaching of alkali and insoluble flakes into the formulation, these can be offset by the choice of an appropriate glass. As the composition of glass formulations may be varied by the amounts and types of sand and silica added and the heat treatment conditions used, the proper container for any formulation can be selected.

New, unused glass containers are tested for resistance to attack by high-purity water using a sulfuric acid titration to determine the amount of released alkali. Both glass and plastic containers are used to protect light-sensitive formulations from degradation. The amount of transmitted light is measured using a spectrometer of suitable sensitivity and accuracy.

Glass is generally available in flint, amber, blue, emerald green and certain light-resistant green and opal colors. The blue-, green- and flint-colored glasses, which transmit ultraviolet and violet light rays, do not meet the official specifications for light-resistant containers.

Colored glass usually is not used for injectable preparations since it is difficult to detect the presence of discoloration and particulate matter in the formulations. Light-sensitive drugs for parenteral use usually are sealed in flint ampuls and placed in a box. Multiple-dose vials should be stored in a dark place.

Manufacturers of prescription drug products should in-

clude sufficient information on their product labels to inform the pharmacist of the type of dispensing container needed to maintain the identity, strength, quality and purity of the product. This brief description of the proper container, eg, light-resistant, well-closed or tight, may be omitted for those products dispensed in the manufacturer's original container.

Plastics—Plastic containers have become very popular for storing pharmaceutical products. Polyethylene, polystyrene, polyvinyl chloride and polypropylene are used to prepare plastic containers of various densities to fit specific formulation needs.

Factors such as plastic composition, processing and cleaning procedures, contacting media, inks, adhesives, absorption, adsorption and permeability of preservatives also affect the suitability of a plastic for pharmaceutical use. Hence, biological test procedures are used to determine the suitability of a plastic for packaging products intended for parenteral use and for polymers intended for use in implants and medical devices. Systemic injection, intracutaneous and implantation tests are employed. In addition, tests for nonvolatile residue, residue on ignition, heavy metals and buffering capacity were designed to determine the physical and chemical properties of plastics and their extracts.

The high-density polyethylene containers, which are used for packaging capsules and tablets, possess characteristic thermal properties, a distinctive infrared absorption spectrum and a density between 0.941 and 0.965 g/cm³. In addition, these containers are tested for light transmission, water-vapor permeation, extractable substances, nonvolatile residue and heavy metals. Where a stability study has been performed to establish the expiration date for a dosage form in an acceptable high-density polyethylene container, any other high-density polyethylene container may be substituted provided that it, too, meets compendial standards and that the stability program is expanded to include the alternate container.

Materials from the plastic itself can leach into the formulation, and materials from the latter can be absorbed onto, into or through the container wall. Various pharmaceutical preservatives are bound by the barrels of some plastic syringes. However, changing the composition of the syringe barrel from nylon to polyethylene or polystyrene has eliminated the binding in some cases.

A major disadvantage of plastic containers is the two-way permeation of "breathing" through the container walls. Volatile oils and flavoring and perfume agents are permeable through plastics to varying degrees. Components of emulsions and creams have been reported to migrate through the walls of some plastics causing either a deleterious change in the formulation or collapse of the container. Loss of moisture from a formulation is common. Gases, such as oxygen or carbon dioxide in the air, have been known to migrate through container walls and affect a preparation.

Solid dosage forms, such as penicillin tablets, when stored in some plastics, are affected deleteriously by moisture penetration from the atmosphere into the container.

Metals—The pharmaceutical industry was, and to a degree still is, a tin stronghold. However, as the price of tin constantly varies, more collapsible aluminum tubes are being used. Lead tubes tend to have pinholes and are little used in the industry.

A variety of internal linings and closure fold seals are available for both tin and aluminum tubes. Tin tubes can be coated with wax or with vinyl linings. Aluminum tubes are available with epoxy or phenolic resin, wax, vinyl or a combination of epoxy or phenolic resin with wax. As aluminum is able to withstand the high temperatures required to cure epoxy and phenolic resins adequately, tubes made from this metal presently offer the widest range of lining possibilities.

Closure foldseals may consist of unmodified vinyl resin or plasticized cellulose and resin with or without added color.

Collapsible tubes are available in many combinations of diameters, lengths, openings and caps. Custom-use tips for ophthalmic, nasal, mastitis and rectal applications also are available. Only a limited number of internal liners and clo-

sure seals are available for tubes fitted with these special-use tips.

Lined tubes from different manufacturers are not necessarily interchangeable. While some converted resin liners may be composed of the same base resin, the actual liner may have been modified to achieve better adhesion, flow properties, drying qualities or flexibility. These modifications may have been necessitated by the method of applying the liner, the curing procedure or, finally, the nature of the liner itself.

Closures

The closures for the formulations also must be studied as a portion of the overall stability program. While the closure must form an effective seal for the container, the closure must not react chemically or physically with the product. It must not absorb materials from the formulation or leach its ingredients into the contents.

The integrity of the seal between the closure and container depends on the geometry of the two, the materials used in their construction, the composition of the cap liner and the tightness with which the cap has been applied. Torque is a measure of the circular force, measured in inch-pounds, which must be applied to open or close a container. When pharmaceutical products are set up on a stability study, the formulation must be in the proposed market package. Thus, they should be capped with essentially the same torque to be used in the manufacturing step.

Rubber is a common component of stoppers, cap liners and parts of dropper assemblies. Sorption of the active ingredient, preservative or other formulation ingredients into the

rubber and the extraction of one or more components of the rubber into the formulation are common problems.

The application of an epoxy lining to the rubber closure reduces the amount of leached extractives but essentially has no effect on the sorption of the preservative from the solution. Teflon-coated rubber stoppers may prevent most of the sorption and leaching.

References

1. Lintner CJ: *Quality Control in the Pharmaceutical Industry*, vol 2, Academic, New York, 141, 1973.
2. Connors KA, Amidon GL, Stella JV: *Chemical Stability of Pharmaceuticals*, 2nd ed, Wiley, New York, 1986.
3. *Current Good Manufacturing Practice*, 21 CFR 211.
4. *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*, FDA, Center for Drugs and Biologics, Office of Drug Research Review, Feb 1987.
5. Lintner CJ et al: *Am Perfum Cosmet* 85 (12): 31, 1970.
6. Kennon L: *J Pharm Sci* 53: 815, 1964.
7. McMinn CS, Lintner CJ (oral presentation), APhA Acad Pharm Sci Mtg Ind Pharm Tech Sec, Chicago IL, May 1973.
8. Bentley DL: *J Pharm Sci* 59: 464, 1970.

Bibliography

- Florey K: *STP Pharma* 2: 236, 1986.
- Lachman L et al: *The Theory and Practice of Industrial Pharmacy*, 2nd ed, Lea & Febiger, Philadelphia, 1976.
- USP XXIII, General Chapter (1077), 1994.
- Wagner JG, ed: *Biopharmaceutics and Relevant Pharmacokinetics*, Hamilton Press, Hamilton IL, 1971.
- Windheuser JJ, ed: *The Dating of Pharmaceuticals*, Univ Extension, Univ Wisconsin, Madison WI, 1970.