20 TH EDITION

Remington: The Science and Practice of Pharmacy

ALFONSO R GENNARO
Chairman of the Editorial Board
and Editor

Editor: Daniel Limmer
Managing Editor: Matthew J. Hauber
Marketing Manager: Anne Smith

Lippincott Williams & Wilkins

351 West Camden Street
Baltimore, Maryland 21201-2436 USA

227 East Washington Square
Philadelphia, PA 19106

The publisher is not responsible (as a matter of product liability, negligence or otherwise) for any injury resulting from any material contained herein. This publication contains information relating to general principles of medical care which should not be construed as specific instructions for individual patients. Manufacturers' product information and package inserts should be reviewed for current information, including contraindications, dosages and precautions.

Printed in the United States of America

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

Library of Congress Catalog Card Information is available
ISBN 0-683-306472

The publishers have made every effort to trace the copyright holders for borrowed material. If they have inadvertently overlooked any, they will be pleased to make the necessary arrangements at the first opportunity.

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.

To purchase additional copies of this book call our customer service department at **(800) 638-3030** or fax orders to **(301) 824-7390.** International customers should call **(301) 714-2324.**

00 01 02 03 04
1 2 3 4 5 6 7 8 9 10

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.

Twentieth Edition—2000

Published in the 180th year of the
PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE

units suitable for small hospitals, laboratories, or pharmacies. In using gas sterilization the possibility of human toxicity must be kept in mind. Care should be taken to restrict exposure to ethylene oxide during the loading, venting, and unloading of the sterilizer. Ethylene oxide sterilization produces irritating by-products that remain as residues in or on the articles sterilized. Residues include ethylene glycol and ethylene chlorohydrin (when in contact with chloride ions) in addition to ethylene oxide itself. To minimize such residues the sterilized articles should be aerated for at least 72 hr, preferably at 40 to 50°.

Ambient aeration time for sterilized polyethylene bottles should be about 48 hr. Ethylene oxide is recommended for the sterilization of solid materials that will not withstand heat sterilization. The FDA has recommended maximum residues in the parts per million range for ethylene oxide, ethylene glycol, and ethylene chlorohydrin.

RADIATION—Sterilization by exposure to ionizing radiation is an acceptable procedure for components of ophthalmic preparations or indeed for the total product, such as certain ophthalmic ointments. Sources of radiation are twofold and include linear electron accelerators and radioisotopes. The linear accelerators produce high-energy electrons with very little penetrating power. Radioisotopes, particularly ^{60}Co, are employed more widely for sterilization. Sterilization by radiation may produce untoward effects such as chemical changes in product components as well as changes in color or physical characteristics of package components.

OPHTHALMIC PREPARATION CHARACTERISTICS

CLARITY—Ophthalmic solutions are by definition free from foreign particles, and clarity normally is achieved by filtration. It is, of course, essential that the filtration equipment be clean and well rinsed so that particulate matter is not contributed to the solution by equipment designed to remove it. Operations performed in clean surroundings, the use of laminar-flow hoods, and proper nonshedding garments will contribute collectively to the preparation of brilliantly clear solutions free from foreign particles. In many instances clarity and sterility may be achieved in the same filtration step. It is essential to realize that solution clarity is equally a function of the cleanliness of the intended container and closure. Both container and closure must be thoroughly clean, sterile, and nonshedding. That is, the container or closure must not contribute particles to the solution during prolonged contact such as shelf-life storage. This normally is established by thorough stability testing.

STABILITY—The stability of a drug in solution, ie, an ophthalmic product, depends on the chemical nature of the drug substance, product pH, method of preparation (particularly temperature exposure), solution additives, and type of packaging. Until two or three decades ago the stability of ophthalmic solutions was an exceedingly short-term concept; generally, it was the time required for a patient to complete the use of 15 or 30 mL of solution. Now, of course, the stability of ophthalmic products is expressed in terms of years. However, 2- to 3-year stability often is achieved only by virtue of compromise.

Drugs such as pilocarpine and physostigmine are both active and comfortable in the eye at a pH of 6.8; however, at this pH chemical stability (or instability) can be measured in days or months. With either drug, a substantial loss in chemical stability will occur in less than 1 year. On the other hand, at pH 5 both drugs are stable for a period of several years.

In addition to optimal pH, if oxygen sensitivity is a factor, adequate stability may require the inclusion of an antioxidant. prove detrimental to stability by permitting oxygen permeation resulting in oxidative decomposition of the drug substance.

The attainment of optimum stability most often imposes a series of compromises on the formulator. The optimum pH may be lower than that preferable for product comfort, although this effect may be minimized by adjusting pH with a buffer of minimum capacity. Additives such as chelating agents and antioxidants may be required, and convenience packaging may diminish shelf life of the product.

It should be stressed that stability refers to total product stability not just the chemical stability of a single product component. That is an oversimplification. A well-planned stability program will consider and evaluate the chemical stability of the active ingredient, chemical stability of the preservative substance, continuing preservative efficacy against selected test organisms, and adequacy of the package as a function of time (ie, does the package protect sterility in addition to various physical measures such as pH, clarity, resuspendability of suspensions, and the like?). One also must support the thesis that the material on test is representative of all lots of a given product.

BUFFER AND pH—Ideally, ophthalmic preparations should be formulated at a pH equivalent to the tear fluid value of 7.4. Practically, this seldom is achieved. The large majority of active ingredients used in ophthalmology are salts of weak bases and are most stable at an acid pH. This generally can be extended to suspensions of insoluble corticosteroids. Such suspensions usually are most stable at an acid pH.

Optimum pH adjustment generally requires a compromise on the part of the formulator. The pH selected should be optimum for stability. The buffer system selected should have a capacity adequate to maintain pH within the stability range for the duration of the product shelf life. Buffer capacity is the key in this situation.

It generally is accepted that a low (acid) pH *per se* necessarily will not cause stinging or discomfort on instillation. If the overall pH of the tears, after instillation, reverts rapidly to pH 7.4, discomfort is minimal. On the other hand, if the buffer capacity is sufficient to resist adjustment by tear fluid and the overall eye pH remains acid for an appreciable period of time, then stinging and discomfort may result. Consequently, buffer capacity should be adequate for stability but minimized so far as possible, to allow the overall pH of the tear fluid to be disrupted only momentarily.

TONICITY—Tonicity refers to the osmotic pressure exerted by salts in aqueous solution. An ophthalmic solution is isotonic with another solution when the magnitudes of the colligative properties of the solutions are equal. An ophthalmic solution is considered isotonic when its tonicity is equal to that of an 0.9% sodium chloride solution.

The calculation of tonicity at one time was stressed rather heavily. The fledgling pharmacist was taught in great detail the requirements of, and means of achieving, exact tonicity, sometimes to the detriment of other factors such as sterility and stability.

In actuality the eye is much more tolerant of tonicity variations than was at one time suggested. The eye usually can tolerate solutions equivalent to a range of 0.5 to 1.8% sodium chloride. Given a choice, isotonicity always is desirable and particularly is important in intraocular solutions. It need not, however, be an overriding concern when total product stability is to be considered.

The tonicity of ophthalmic (and parenteral) solutions has been investigated intensively over the years. These studies have resulted in the accumulation and publication of a large number of sodium chloride equivalents that are useful in calculating tonicity values. See Chapter 18.

VISCOSITY—The USP permits the use of viscosity-increasing agents to prolong contact time in the eye and thus enhance drug absorption and activity. Substances such as