Symposium on

Ocular Therapy

Vol. 9

Edited by

IRVING H. LEOPOLD
ROBERT P. BURNS

VOLUME NINE

Symposium on

Ocular Therapy

Under the auspices of the American Academy of Ophthalmology and Otolaryngology and the Association for Research in Vision and Ophthalmology

Edited by

IRVING H. LEOPOLD, M.D., D.Sc. (Med.)

Professor and Chairman, Department of Ophthalmology
California College of Medicine
University of California
Irvine, California

ROBERT P. BURNS, M.D.

Professor, Department of Ophthalmology
University of Oregon Health Sciences Center
Portland, Oregon

A WILEY MEDICAL PUBLICATION

JOHN WILEY & SONS

New York • London • Sydney • Toronto

Volumes One through Seven are available from the C. V. Mosby Company

Library of Congress Cataloging in Publication Data:

Main entry under title:

Ocular therapy.

(A Wiley medical publication)
Vols. 1–2 "from Symposia on Ocular Drug Complications and Management held under the auspices of the American Academy of Ophthalmology and Otolaryngology," in San Francisco, 1964, and in Chicago, 1965 and 1966.
Vols. 3– with title "Symposium on Ocular Therapy, under the auspices of the American Academy of Ophthalmology and Otolaryngology and the Association for Research in Ophthalmology.
Vols. 7–9 under the auspices of the American Academy of Ophthalmology and Otolaryngology and the Association for Research in Vision and Ophthalmology.
Vols. 8– edited by I. H. Leopold and R. P. Burns.
Vols. 8– published by Wiley, New York.
Includes bibliographies.
1. Therapeutics, Ophthalmological—Congresses. 2. Ocular pharmacology—Congresses. I. Leopold, Irving H. ed. II. Burns, Robert P., 1923– III. Symposium on Ocular Therapy. IV. American Academy of Ophthalmology and Otolaryngology. V. Association for Research in Ophthalmology. VI. Association for Research in Vision and Ophthalmology. [DNLM: 1. Eye diseases—Drug therapy. 2. Ophthalmology—Congresses. W3 SY5365/ H2Ve v. 3-7]
RE991.033 617'.7'06 66-22972
ISBN 0-471-01717-5 (v. 9)

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

Contributors

Thomas R. Arendshorst, M.D.

University of Oregon Health Sciences Center, Portland, Oregon 97201

Bernard Becker, M.D.

Washington University School of Medicine, St. Louis, Missouri 63110

Robert P. Burns, M.D.

University of Oregon Health Sciences Center, Portland, Oregon 97201

Andrew J. Cottingham, Jr., M.D.

Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Florida 33152

Donald J. Doughman, M.D.

Department of Ophthalmology, University of Minnesota, Minneapolis, Minnesota 55455

Richard K. Forster, M.D.

Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Florida 33152

Fredrick T. Fraunfelder, M.D.

Department of Ophthalmology, University of Arkansas Medical School, Little Rock, Arkansas 72201

Scott Goodnight, M.D.

University of Oregon Health Sciences Center, Portland, Oregon 97201

John E. Harris, Ph.D., M.D.

Department of Ophthalmology, University of Minnesota, Minneapolis, Minnesota 55455

Michael A. Kass, M.D.

Washington University School of Medicine, St. Louis, Missouri 63110

Herbert E. Kaufman, M.D.

Department of Ophthalmology, University of Florida College of Medicine, Gainesville, Florida 32610

Steven G. Kramer, M.D., Ph.D.

Professor and Chairman, Department of Ophthalmology, University of California, San Francisco, California 94143

Alan M. Laties, M.D.

Department of Ophthalmology, Scheie Eye Institute, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania 19104

Irving H. Leopold, M.D., D.Sc. (Med.)

Professor of Ophthalmology, California College of Medicine, University of California, Irvine, California 92664

Yuri F. Maichuk, M.D., D.Sc. (Med.)

Virus Eye Diseases Department, Moscow Helmholtz Institute of Ophthalmology, Moscow, U.S.S.R.

David M. Maurice, Ph.D.

Department of Surgery, Division of Ophthalmology, Stanford University Medical Center, Stanford, California 94305

Deborah Pavan-Langston, M.D.

Massachusetts Eye and Ear Infirmary, Boston, Massachusetts 02114

Ira A. Priluck, M.D.

Department of Ophthalmology, University of Minnesota, Minneapolis, Minnesota 55455

Kenneth C. Swan, M.D.

University of Oregon Health Sciences Center, Portland, Oregon 97201

Peter Wright, F.R.C.S.

Moorfields Eye Hospital, Kings College Hospital, London, England

Ihor G. Zachary, M.D.

Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami School of Medicine, Miami, Florida 33152

Preface

These symposia were started over a decade ago in an effort to provide current information on drug therapy in ophthalmology. During this period many areas have been reviewed, new information considered, and practical management of a variety of ocular conditions with selected pharmacologic agents detailed. Each participant has attempted to present his material in concise and lucid fashion.

Each symposium is the responsibility of the Drug Committee of the Academy of Ophthalmology and Otolaryngology and has had the full cooperation of the Association for Research in Vision and Ophthalmology. The symposia are a joint effort of the two groups.

The transactions of this symposium are the work of joint editorship as in Volume 8. There is an increase in material provided. The volume has increased in size representing an enlargement in the number of subjects considered. Part of this increase is due to the inclusion of Professor Yuri F. Maichuk's discussion of drug delivery systems. This year, as well as in future years, other internationally recognized authorities will contribute current information concerning a particular area of ophthalmological interest. It is hoped that, by presenting the progress in pharmacology and therapeutics as applied to ophthalmology, visual loss can be prevented.

IRVING H. LEOPOLD, M.D.,D.SC. (MED.)
ROBERT P. BURNS, M.D.

Irvine, California
Portland, Oregon
February 1976

Symposium on

Ocular Therapy

There is no such thing as a patriotic art or patriotic science. Both art and science belong, like every higher good, to all the world and can be fostered only by the free flow of mutual influence among all contemporaries, with constant regard for all we have and know of the past.

Goethe

Professor Yuri F. Maichuk, of the Moscow Helmholtz Institute of Ophthalmology in the Soviet Union, is the first honored foreign guest of the American Academy of Ophthalmology's Committee on Drugs. This *Symposium on Ocular Therapy*, sponsored by the academy in conjunction with the Association for Research in Vision and Ophthalmology, seeks to broaden our views of ophthalmic problems, not only of the United States, but of the world.

Professor Maichuk is ideally fitted to add to our global knowledge. Educated in Lvov, in the Ukraine, he became a physician in 1951 and an ophthalmologist in 1954. In 1955 he entered trachoma research and since 1965 has been at the Moscow Helmholtz Institute of Ophthalmology as head of the Virus Eye Diseases Department. He received a D.Sc. degree in medicine in 1967 and became a professor of ophthalmology in 1971.

Professor Maichuk initiated his learning of English after age 30. He has published 120 articles and two books, mainly on antibiotics and virus eye disease. Widely traveled, he is a member of numerous ophthalmologic societies. He is currently on leave from his duties to serve with the World Health Organization's Expert Advisory Panel on Trachoma and Onchocerciasis. Being familiar with both old and new methods of eye disease treatment, he is an ideal person to educate American ophthalmologists to world problems.

Contents

Chapter 1

Polymeric drug delivery systems in ophthalmology

Yuri F. Maichuk, M.D., D.Sc. (Med.)

Many techniques are utilized to improve the response to drugs that are delivered topically to the eye. As far back as the turn of this century, ophthalmologists displayed active interest in the problem of precise dosage of topically administered drugs and prolongation of their therapeutic effect. Despite this objective, most ophthalmic preparations have traditionally been applied as drops or ointments, although accurate dosing of agents is not possible in these forms. Eyedrops persist in the conjunctival sac for a short time and are washed out rapidly by reflex tear flow, particularly if the drops are an irritant. Therefore, to attain a therapeutic effect, they should be applied frequently, at least five to eight times daily. The lid, conjunctiva, and cornea can exhibit irritative or allergic phenomena in response to frequent application of drugs. Fortunately, the eye cannot be overdosed at any single treatment by eyedrops or ointments, because the excess is immediately squeezed out. In this way, however, the effect of up to 90% of ophthalmic preparations is lost. Ointments also cause mistiness of vision that may interfere with the patient's work. Ointments tend to spread onto the skin of the eyelids and are therefore more likely to cause contact dermatitis, either to an ingredient of the ointment base or to active preparations.

Development of more pharmaceutical agents for ophthalmic practice is a promising way to attain precision in dosage of preparations and to prolong their effect. In addition to ensuring more rational procedures for application of chemotherapeutic agents, a solution of the problem of prolonging drug effect will contribute to the establishment and maintenance of optimal therapeutic concentrations of eye tissue preparations over a long period.

This report summarizes the results of experimental and chemical studies carried out in the

Moscow Helmholtz Ophthalmological Institute on the following four polymeric drug delivery systems:

Polyvinyl alcohol vehicle	PVAV
Polyacrylamide vehicle	PAAV
Polyvinyl alcohol inserts	PVAI
Soluble ophthalmic drug inserts	SODI

EXPERIMENTAL STUDIES

Polyvinyl alcohol vehicle (PVAV)

To tackle the problem of prolongation, a synthetic vehicle, polyvinyl alcohol (PVA), is the most popular viscosity-increasing agent used in ophthalmic preparations.[1-4] The advantages of the PVA vehicle over aqueous vehicle ointments and oily suspensions are as follows:

Prolonging effect of the drug and higher concentration level
Better penetration into eye tissues and media
Extended persistence of activity of unstable drugs
Reduction of drug toxicity
Absence of tissue irritation
Good therapeutic results achieved with reduced frequency of drug administration

The following paragraph may illustrate some of these points. Antibiotic activity in the conjunctival sac after a single instillation of antibiotic in a PVA vehicle is at a higher level than are applications in aqueous vehicles and ointments (Table 1-1, Figure 1-1). Aqueous and tissue levels of antibiotics and sulfonamides in rabbits are higher when drugs are used on the PVAV (Figure 1-2). The PVAV enhances penetration of the drug into the eye; 3 hr

Table 1-1. Oletetrine levels in rabbit conjunctival sac after administration in ointment, aqueous solutions, and PVAVs

	Average concentration in U/ml		
Hours after dose	*Aqueous solution*	*Ointment*	*PVAV*
1	27.6 (± 2.0)	76.4 (± 5.0)	115.9 (± 19.2)
3	4.7 (± 0.2)	10.2 (± 0.7)	14.8 (± 1.3)
6	1.1[a]	1.1 (± 0.3)	5.3 (± 0.3)
9	0.4[a]	0.3[a]	1.8 (± 0.2)
12	0.3[a]	0.3[a]	1.3 (± 0.2)
24	0.1[a]	0.1[a]	0.8 (± 0.2)

[a] Zero in more than 50% of tests.

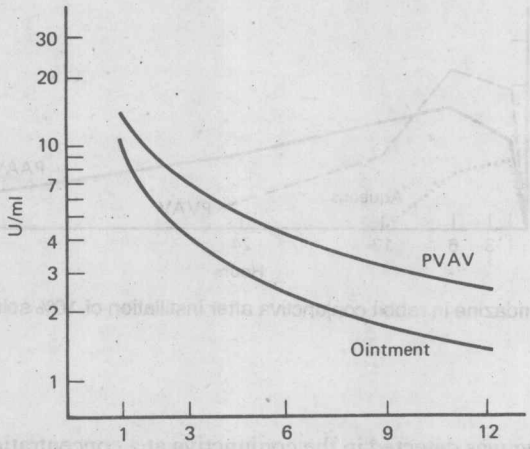

Figure 1-1. Monomycin in rabbit conjunctival sac (U/ml) after single administration in 1% PVAV and in 1% ointment.

after instillation of erythromycin in aqueous solution and in PVAV, the respective concentrations in the rabbit aqueous humor were 0.2 and 0.8 U/ml.[5]

Several ophthalmic drugs were prepared on a 2.5% PVAV for clinical study: antibiotics (tetracycline, erythromycin, oletetrine, neomycin, monomycin, kanamycin, polymyxin B, glutamicin, nystatin, levorin), sulfonamides (short-acting ethazole and long-acting sulfapyridazine), idoxuridine, pilocarpine, dexamethasone, and others.

Polyacrylamide vehicle (PAAV)

Polyacrylamide is another synthetic vehicle that provides an even more prolonged drug effect than does the PVAV.[6] After a single instillation of 10% sulfapyridazine solution in

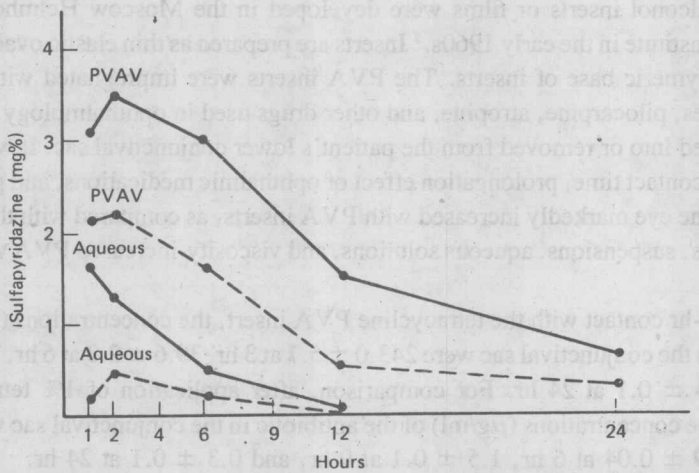

Figure 1-2. Sulfapyridazine in rabbit conjunctiva (—) and cornea (---) after instillation of 10% aqueous or PVAV solutions.

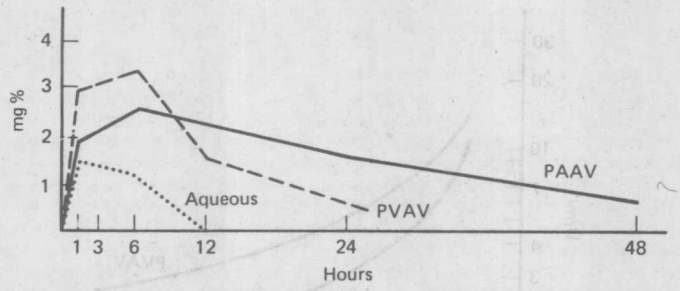

Figure 1-3. Sulfapyridazine in rabbit conjunctiva after instillation of 10% solution in aqueous vehicle, PVAV and PAAV.

1% PAAV, the drug was detected in the conjunctiva at a concentration of 1.66 mg% 24 hr later and at 0.58 mg% 48 hr later (Figure 1-3). When the PVAV was used instead, the respective concentration at 24 hr was 0.58 mg%. One percent and 5% PAAVs showed almost the same prolonged drug effect; the respective concentrations of sulfapyridazine at 24 hr in the conjunctiva were 1.66 and 1.82 mg% and in the cornea 0.74 and 0.82%. Studies in rabbits demonstrated that the PAAV had a superior conjunctival contact time, but this value was approximately the same for 1 and 5% solutions of PAA.

One percent PAAV and ophthalmic drug[5] on PAAV are well tolerated by the eye during long courses of drug administration. Histologic examinations of rabbit eyes showed no changes or abnormalities.

Pharmaceutical, chemical, and microbiologic analysis of 1% PAA solutions of antibiotics (neomycin, kanamycin), sulfonamides (ethazole, sulfapyridazine), idoxuridine, pilocarpine, atropine, dicain, and dexamethasone demonstrated drug stability against sterilization and storage up to 24 months.

Polyvinyl alcohol insert (PVAI)

Polyvinyl alcohol inserts or films were developed in the Moscow Helmholtz Ophthalmological Institute in the early 1960s.[7] Inserts are prepared as thin elastic oval plates. PVA was the polymeric base of inserts. The PVA inserts were impregnated with antibiotics, sulfonamides, pilocarpine, atropine, and other drugs used in ophthalmology. Inserts were easily slipped into or removed from the patient's lower conjunctival sac. It was found that the surface contact time, prolongation effect of ophthalmic medications, and penetration of drugs into the eye markedly increased with PVA inserts, as compared with the application of ointments, suspensions, aqueous solutions, and viscosity-increased PVAV (Figure 1-4, Table 1-2).

After a 3-hr contact with the tetracycline PVA insert, the concentrations (μg/ml) of the antibiotic in the conjunctival sac were 243.0 ± 5.7 at 3 hr, 39.6 ± 2.3 at 6 hr, 7.7 ± 1.0 at 9 hr, and 3.4 ± 0.1 at 24 hr. For comparison, after application of 1% tetracycline oily solution, the concentrations (μg/ml) of the antibiotic in the conjunctival sac were 3.7 ± 01 at 3 hr, 1.9 ± 0.04 at 6 hr, 1.5 ± 0.1 at 9 hr, and 0.3 ± 0.1 at 24 hr.

After a single application of monomycin, the following average antibiotic levels in rabbit

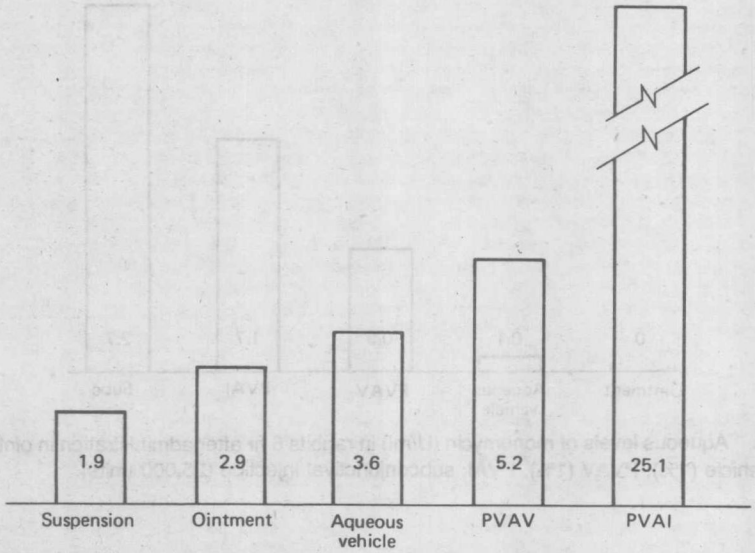

Figure 1-4. Tetracycline in rabbit conjunctival sac (U/ml) 6 hr after a single administration in various vehicles and in PVAIs.

Table 1-2. Tetracycline levels (U/ml) in conjunctival sac in rabbits and trachoma patients after administration of PVAI

Hours after dose	*Rabbits*	*Trachoma patients*
3	72.0 (± 4.9)	243.0 (± 5.7)
6	25.1 (± 4.3)	39.6 (± 2.3)
9	5.6 (± 0.8)	7.7 (± 1.0)
24	2.5 (± 0.6)	3.4 (± 0.1)

aqueous humor at 6 hr were obtained: PVA insert, 1.7 U/ml; PVAV, 0.9 U/ml; aqueous solution, 0.1 μ/ml; ointment, 0. For comparison, after injection of 25,000 U of monomycin subconjunctivally, the antibiotic level in aqueous humor at 6 hr was 2.7 U/ml (Figure 1-5). The use of PVA inserts provides continuous release, higher grade levels, and better penetration into the eye and therefore may replace subconjunctival injection in certain cases. Clinical observations have demonstrated the marked therapeutic efficacy of PVA inserts in treatment of bacterial conjunctivitis, keratitis, trachoma, and glaucoma.[4]

It was observed that the PVA inserts,[8] like some other ocular inserts,[9,20] did not dissolve in the conjunctival sac, and this necessitated their removal from the sac. This disadvantage makes for limited clinical use of PVA inserts.

Soluble ophthalmic drug insert (SODI)

Soluble ophthalmic drug inserts have been suggested and developed at the Moscow Helmholtz Ophthalmological Institute by the present author in collaboration with G. Khromov of the All-Union Research Institute for Medical Equipment, USSR. Following the results of an experimental study and clinical trial, SODIs were endorsed for use in

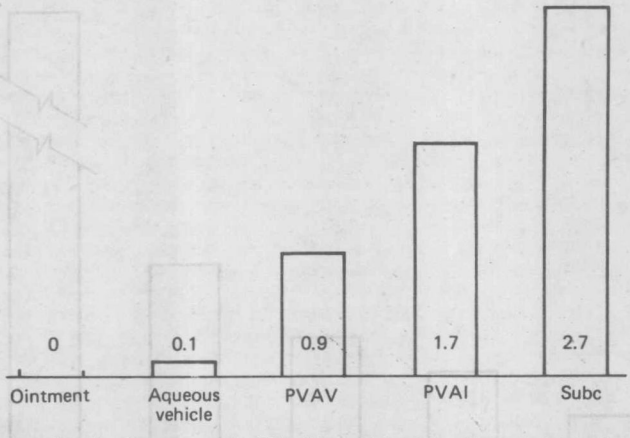

Figure 1-5. Aqueous levels of monomycin (U/ml) in rabbits 6 hr after administration in ointment (1%), aqueous vehicle (1%), PVAV (1%), PVAI, subconjunctival injection (25,000 units).

ophthalmic practice in the USSR by a June 11, 1971 decision of the Pharmacological Committee, Ministry of Health. SODIs are prepared as thin elastic oval plates approximately 9 × 4.5 × 0.2–0.3 mm (Figure 1-6). SODIs are made from polymers and copolymers, such as polyacrylamide, ethyl acrylate, and vinylpyrrolidone.[15] In selecting the type of polymer used, the main criteria were eye tolerance, solubility, and prolonging drug effect. Apart from homopolymers, more than 20 copolymers were tested (Tables 1-3).

An experimental study demonstrated that SODIs were well tolerated by rabbit eyes. No irritant or toxic effects were noted either during the treatment course or much later, nor were any histologic changes detected.

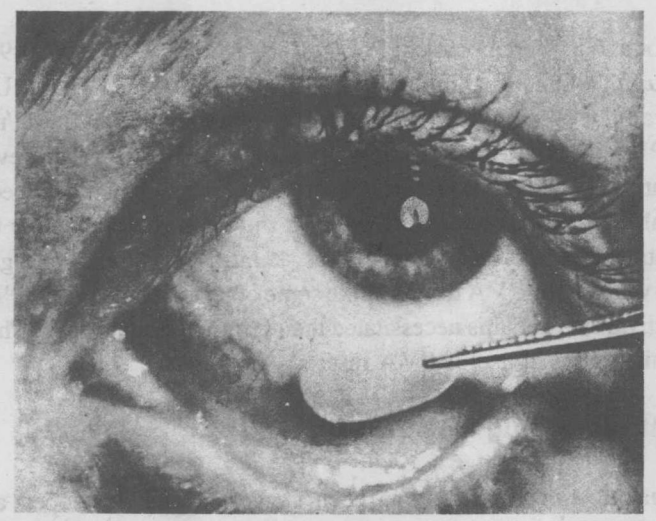

Figure 1-6. Application of SODI.

Table 1-3. Conjunctival and corneal levels (mg%) of neomycin and sulfapyridazine in rabbits in 24 hr after administration

Polymeric base of ophthalmic inserts	*Sulfapyridazine*		*Neomycin*	
	Conjunctiva	*Cornea*	*Conjunctiva*	*Cornea*
Polyvinylpyrrolidone	0.62	0.18	Trace	0
PVA	0.58	0.36	0.20	0
PAA	1.56	0.65	0.75	Trace
Copolymers, PAA	2.05	0.85	1.15	0.18
Copolymers, PAA + PVA	1.70	0.60	0.63	0.10
Control (aqueous solution)	0	0	0	0

The contact time of nickel chloride on the conjunctiva, when incorporated into SODI, was taken as an indicator of the surface contact time for the vehicle (nickel test). One group of rabbits received SODI, and another group, which served as a control, received a single instillation on nickel chloride in water solution at an identical concentration (Figure 1-7). It was found that, when SODIs were used, the surface contact time was much longer than with administration in aqueous solution of polyvinylpyrrolidone vehicle, PAAV, or PVAI.

Experimental and clinical studies have been completed with SODIs impregnated with neomycin, kanamycin, sulfapyridazine, idoxuridine, florenal, atropine, pilocarpine, dexamethasone, dicain, and some combinations of them. The method for obtaining SODIs has the advantage that it avoids significant variations in their weight, and drug dosages are thus more precise. Routine pharmaceutical quality tests were used to estimate changes in weight of SODI and changes in the shape, color, water absorption, mechanical robustness, dissolution rate, and in amount of active material (Table 1-4). The drug content of SODI is invariable; it is 2.6 mg for pilocarpine, 1.59 mg for atropine, 1.12 mg for neomycin, 1.22 mg for kanamycin, 5.25 mg for sulfapyridazine, 0.75 for dicain, and 1.70 for idoxuridine.

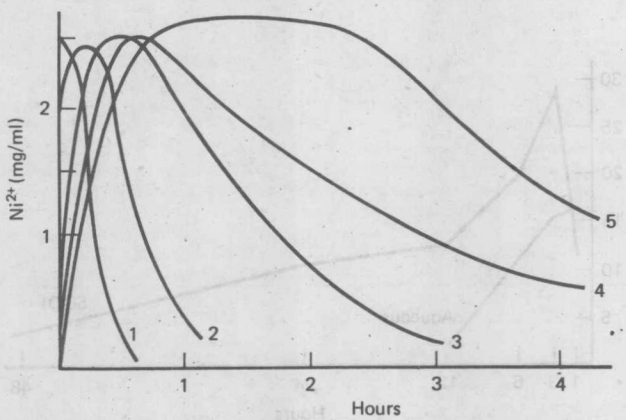

Figure 1-7. Nickel test for conjunctival surface contact time after administration of nickel chloride in (1) aqueous vehicle, (2) polyvinylpyrrolidone vehicle, (3) PAAV, (4) PVAI, (5) SODI.