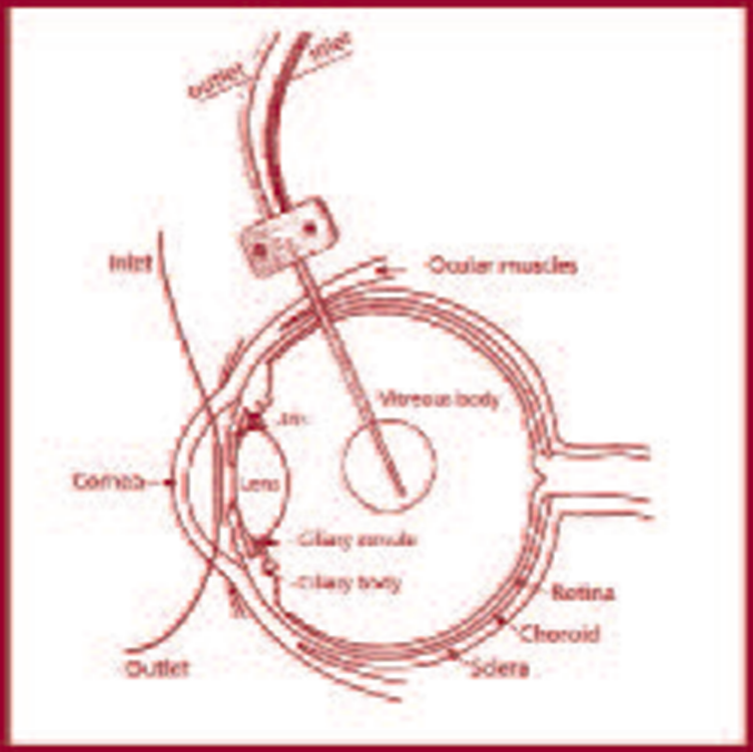
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 130

Ophthalmic Drug Delivery Systems

Second Edition, Revised and Expanded



edited by
Ashim K. Mitra

Ophthalmic Drug Delivery Systems

Second Edition, Revised and Expanded

edited by

Ashim K. Mitra

University of Missouri–Kansas City
Kansas City, Missouri, U.S.A.

MARCEL DEKKER, INC. NEW YORK • BASEL

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress.

ISBN: 0-8247-4124-2

This book is printed on acid-free paper.

Headquarters
Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution
Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 41-61-260-6300; fax: 41-61-260-6333

World Wide Web
http://www.dekker.com

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above.

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

Foreword

For new medications to be used effectively, and for those now available to provide maximal benefit, improvements in ocular drug delivery are essential. Drug delivery is no less vital than drug discovery.

Although many drugs can be safely delivered by eye drops, effective treatment depends on patient compliance. Non-compliance is a major problem, especially in poorly educated patients and patients who are required to apply drops frequently. Lack of compliance frequently results in suboptimal therapeutics, which may lead to blindness. People with chronic conditions or debilitating disease find complicated eye drop regimens to be a serious handicap.

Even when drugs can be delivered through the cornea and conjunctiva, concentrations may be suboptimal and the therapeutic effect minimal. In the past, a variety of approaches to topical drug delivery have been tested, including gelatin wafers or soft contact lenses soaked in drugs and placed on the cornea or in the cul-de-sac, corneal collagen shields, and iontophoresis. The diversity of these approaches is an indication of the need for a superior method of topical drug delivery and a testament to the fact that no uniformly acceptable method has been developed to date. Currently, vehicles and carriers such as liposomes and substances that gel, as well as nanoparticles, are being evaluated. Also, prodrugs, such as medicines that hydrolyze within the eye, are being developed to achieve higher concentrations, prolonged activity, and reduced toxicity of topically applied medications. These important techniques and others are considered in this book.

Perhaps even more important than surface delivery is the need to apply medications to the posterior segment of the eye. Treatment of blinding posterior segment diseases, including uveitis, proliferative retinopathy, and macular degeneration, requires drug delivery to the retina, the choroid, or the ciliary body in a safe and convenient way. Systemic delivery that can localize to the retina may be possible. Improving scleral permeability may be important for periocular delivery, and devices inserted into the vitreous have certainly been valuable. Both nonbiodegradable controlled-release devices and biodegradable implants inserted into both aqueous and vitreous show great promise.

Posterior segment drug delivery is also becoming important for gene therapy. The need to deliver polypeptide medications and DNA inhibitors has become clear. The challenge of understanding the pharmacokinetics of the drug is matched by the challenge of providing a delivery system that can provide optimal duration of drug delivery in therapeutically sufficient concentrations and still be safe and convenient for the patient.

Our approaches to these goals are imperfect at present, but this critically important book describes in vital detail and with great clarity the progress that has been made so far and the course that needs to be pursued in the future. In my pharmacological memory, it does not seem so long ago that we had no treatment for viral diseases, pilocarpine was the only treatment for glaucoma, and antibiotics were crude and relatively ineffective. Similarly, our present achievements in the field of ocular drug delivery may seem equally primitive as we follow the paths to future progress detailed in this book.

Herbert E. Kaufman, M.D.
Boyd Professor of Ophthalmology, Pharmacology, and Microbiology
Louisiana State University Health Sciences Center
New Orleans, Louisiana, U.S.A.

Preface

A major goal of pharmacotherapeutics is the attainment of an effective drug concentration at the intended site of action for a desired length of time. Efficient delivery of a drug while minimizing its systemic and/or local side effects is the key to the treatment of ocular diseases. The unique anatomy and physiology of the eye offer many challenges to developing effective ophthalmic drug delivery systems, but the knowledge in this field is rapidly expanding. Systems range from simple solutions to novel delivery systems such as biodegradable polymeric systems, corneal collagen shields, iontophoresis, and viral and nonviral gene delivery systems, to name a few. An increase in our understanding of ocular drug absorption and disposition mechanisms has led to the development of many of these new systems.

The first edition of this book laid the foundation necessary for understanding barriers to ophthalmic drug delivery and to review the conventional systems available and/or in various stages of research and development. Since then, significant advances have been made in understanding the molecular mechanisms involved in ocular drug transport. The book begins with a brief discussion on the anatomy and physiology of the eye relevant to ocular drug delivery. The latest techniques, such as microdialysis, and models developed to study ocular drug disposition are discussed. A review of both the conventional and novel delivery systems follows. The book stresses the fact that simple instillation of drug solution in the cul-de-sac is not always acceptable and emphasizes the need for the development of newer and more efficient systems. The book concludes with

the basic information required for pharmaceutical scientists to protect their inventions.

Part I investigates the fundamental considerations in ocular drug delivery. The three chapters in this part review the relevant ocular anatomy and physiology, the constraints imposed by the eye upon successful delivery, and the associated ion and solute transport processes in the eye. They provide information on the various transport processes as well as recently identified drug efflux pumps, which regulate the transport of endogenous and exogenous substances.

Part II opens with a discussion of pharmacokinetics relevant to ocular drug delivery. The next chapter discusses the pharmacokinetic processes guiding the ocular disposition and expands on the pharmacokinetic/pharmacodynamic modeling processes to determine the appropriate dosage regimen. This chapter is followed by a detailed discussion of the various mathematical models developed to describe the distribution and elimination of drugs from the vitreous. This part also includes chapters dealing with the application of microdialysis technique to study ocular drug delivery and disposition, and the applicability of the microdialysis sampling approach for the examination of ocular pharmacokinetics and dynamics of ophthalmics.

Part III is divided into conventional and advanced drug delivery systems. The first section deals with such conventional systems as collagen shields, iontophoresis, microparticulates, and dendrimers. These chapters have been updated to include advances in ocular drug delivery achieved in the past decade. The second section examines the delivery of macromolecules to treat various ocular pathologies. The reader will find more information on the recent developments in animal models of retino-choroidal diseases. The viral and nonviral gene delivery systems introduced in this section are still in their infancy but have the potential to provide enormous therapeutic benefits. This section also focuses on the advances in treating retinal degenerative diseases. The last chapter in this section discusses the principles and delivery aspects of gene, oligonucleotide, and ribozyme therapy.

Part IV provides information on regulatory and patent considerations. Pharmaceutical scientists will gain knowledge of the regulations governing animal and human testing and ultimately the release of the product commercially for public use. The final chapter conveys the legal issues involved in protecting inventions and the basic legal requirements for obtaining patents.

Ashim K. Mitra

Contents

Contributors

Imran Ahmed, Ph.D. Pfizer Global R&D—Groton Laboratories, Groton, Connecticut, U.S.A.

Hemant Alur, Ph.D. Murty Pharmaceuticals, Inc., Lexington, Kentucky, U.S.A.

James E. Chastain, Ph.D. Alcon Research, Ltd., Forth Worth, Texas, U.S.A.

Yu-Ling Cheng, Ph.D. Department of Chemical Engineering and Applied Chemistry, University of Toronto, Toronto, Canada

Nandita G. Das Department of Pharmaceutical Sciences, Idaho State University, Pocatello, Idaho, U.S.A.

Sudip K. Das, Ph.D. Department of Pharmaceutical Sciences, Idaho State University, Pocatello, Idaho, U.S.A

Surajit Dey Department of Pharmaceutical Sciences, University of Missouri–Kansas City, Kansas City, Missouri, U.S.A

Clapton S. Dias Department of Pharmaceutical Sciences, University of Missouri–Kansas City, Kansas City, Missouri, U.S.A

Stuart Friedrich, Ph.D. Department of Chemical Engineering and Applied Chemistry, University of Toronto, Toronto, Canada

Shiro Higaki, M.D. Department of Ophthalmology, LSU Eye and Vision Center of Excellence, Louisiana State University Health Science Center, New Orleans, Louisiana, U.S.A.

James M. Hill, Ph.D. Department of Ophthalmology, LSU Eye and Vision Center of Excellence, Louisiana State University Health Science Center, New Orleans, Louisiana, U.S.A.

Patrick M. Hughes, Ph.D. Allergan Pharmaceuticals, Irvine, California, U.S.A.

Thomas P. Johnston, Ph.D. Department of Pharmaceutical Sciences, University of Missouri–Kansas City, Kansas City, Missouri, U.S.A

Nelson L. Jumbe Albany Medical College, Albany, New York, and Amgen Inc., Thousands Oaks, California, U.S.A.

Uday B. Kompella, Ph.D. Department of Pharmaceutical Sciences and Ophthalmology, University of Nebraska Medical Center, Omaha, Nebraska, U.S.A

Murali K. Kothuri Department of Pharmaceutical Sciences, Idaho State University, Pocatello, Idaho, U.S.A.

Ramesh Krishnamoorthy, Ph.D. Formulation Development, Inspire Pharmaceuticals, Durham, North Carolina, U.S.A.

D. Scott Krueger, Ph.D. Regulatory Affairs, Alcon Research, Ltd., Fort Worth, Texas, U.S.A.

Thomas Wai-Yip Lee, B. Pharm. School of Pharmacy, University of Wisconsin–Madison, Madison, Wisconsin, U.S.A.

Jeannette M. Loutsch, Ph.D. Department of Ophthalmology, LSU Eye and Vision Center of Excellence, Louisiana State University Health Science Center, New Orleans, Louisiana, U.S.A.

Sreeraj Macha, Ph.D.* Department of Pharmaceutical Sciences, University of Missouri–Kansas City, Kansas City, Missouri, U.S.A.

Michael H. Miller Albany Medical College, Albany, New York, U.S.A.

Keith J. Miller Bristol–Myers Squibb Company, Pennington, New Jersey, U.S.A.

Ashim K. Mitra, Ph.D. Department of Pharmaceutical Sciences, University of Missouri–Kansas City, Kansas City, Missouri, U.S.A.

Marvin E. Myles, Ph.D. Department of Ophthalmology, LSU Eye and Vision Center of Excellence, Louisiana State University Health Science Center, New Orleans, Louisiana, U.S.A.

Desiree Ong Department of Ophthalmology, LSU Eye and Vision Center of Excellence, Louisiana State University Health Science Center, New Orleans, Louisiana, U.S.A.

Swathi Pinnamaneni† Department of Pharmaceutical Sciences, Idaho State University, Pocatello, Idaho, U.S.A.

Leena Pitkänen, Lic. Med. Department of Pharmaceutics, University of Kuopio, and Department of Ophthalmology, Kuopio University Hospital, Kuopio, Finland

Kay D. Rittenhouse, Ph.D. Nonclinical Drug Safety, Global Research and Development, La Jolla Laboratories, Pfizer Inc., San Diego, California, U.S.A.

Joseph R. Robinson, Ph.D. School of Pharmacy, University of Wisconsin–Madison, Madison, Wisconsin, U.S.A.

Robert E. Roehrs, Ph.D.‡ Alcon Research, Ltd., Fort Worth, Texas, U.S.A.

* *Current affiliation*: Boehringer Ingelheim Inc., Ridgefield, Connecticut, U.S.A.
† *Current affiliation*: Exploratory Biopharmaceutics and Stability, Bristol-Myers Squibb Company, New Brunswick, New Jersey, U.S.A.
‡ Retired.

Lotta Salminen, M.D. Department of Ophthalmology, University of Tampere, and Department of Ophthalmology, Tampere University Hospital, Tampere, Finland

Bradley Saville, Ph.D. Department of Chemical Engineering and Applied Chemistry, University of Toronto, Toronto, Canada

Ronald D. Schoenwald, Ph.D. College of Pharmacy, The University of Iowa, Iowa City, Iowa, U.S.A.

Gangadhar Sunkara, Ph.D[*] Department of Pharmaceutical Sciences, University of Nebraska Medical Center, Omaha, Nebraska, U.S.A.

Joyce Tombran-Tink, Ph.D. Department of Pharmaceutical Sciences, University of Missouri–Kansas City, Kansas City, Missouri, U.S.A.

Arto Urtti, Ph.D. Department of Pharmaceutics, University of Kuopio, Kuopio, Finland

[*] *Current affiliation*: Clinical Pharmacology Division, Novartis Pharmaceuticals, East Hanover, New Jersey, U.S.A.

1
Overview of Ocular Drug Delivery

Sreeraj Macha* **and Ashim K. Mitra**
University of Missouri–Kansas City, Kansas City, Missouri, U.S.A.

Patrick M. Hughes
Allergan Pharmaceuticals, Irvine, California, U.S.A.

I. INTRODUCTION

Opthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientist. The anatomy, physiology, and biochemistry of the eye render this organ highly impervious to foreign substances. A significant challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage. Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. Potent immunosuppressant therapy in transplant patients and the developing epidemic of acquired immunodeficiency syndrome have generated an entirely new population of patients suffering virulent uveitis and retinopathies. Conventional ophthalmic solution, suspension, and ointment dosage forms no longer constitute optimal therapy for these indications. Research and development efforts to design better therapeutic systems particularly targeted to posterior segment are the primary focus of this text.

The goal of pharmacotherapeutics is to treat a disease in a consistent and predictable fashion. An assumption is made that a correlation exists between the concentration of a drug at its intended site of action and the resulting pharmacological effect. The specific aim of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for

Current affiliation: Boehringer Ingelheim Inc., Ridgefield, Connecticut, U.S.A.

the appropriate duration. Ocular disposition and elimination of a therapeutic agent is dependent upon its physicochemical properties as well as the relevant ocular anatomy and physiology (1). A successful design of a drug delivery system, therefore, requires an integrated knowledge of the drug molecule and the constraints offered by the ocular route of administration.

The active sites for the antibiotics, antivirals, and steroids are the infected or inflamed areas within the anterior as well as the posterior segments of the eye. Receptors for the mydriatics and miotics are in the iris ciliary body. A host of different tissues are involved, each of which may pose its own challenge to the formulator of ophthalmic delivery systems. Hence, the drug entities need to be targeted to many sites within the globe.

Historically, the bulk of the research has been aimed at delivery to the anterior segment tissues. Only recently has research been directed at delivery to the tissues of the posterior globe (the uveal tract, vitreous, choroid, and retina).

The aim of this chapter is merely to present the challenges of designing successful ophthalmic delivery systems by way of introduction. The reader is referred to specific chapters within this book for a thorough discussion of the topic introduced in this section.

II. MECHANISMS OF OCULAR DRUG ABSORPTION

Topical delivery into the cul-de-sac is, by far, the most common route of ocular drug delivery. Adsorption from this site may be corneal or noncorneal. A schematic diagram of the human eye is depicted in Figure 1. The so-called noncorneal route of absorption involves penetration across the sclera and conjunctiva into the intraocular tissues. This mechanism of absorption is usually nonproductive, as drug penetrating the surface of the eye beyond the corneal-scleral limbus is taken up by the local capillary beds and removed to the general circulation (2). This noncorneal absorption in general precludes entry into the aqueous humor.

Recent studies, however, suggest that noncorneal route of absorption may be significant for drug molecules with poor corneal permeability. Studies with inulin (3), timolol maleate (3), gentamicin (4), and prostaglandin $PGF_{2\alpha}$ (5) suggest that these drugs gain intraocular access by diffusion across the conjunctiva and sclera. Ahmed and Patton (3) studied the noncorneal absorption of inulin and timolol maleate. Penetration of these agents into the intraocular tissues appears to occur via diffusion across the conjunctiva and sclera and not through reentry from the systemic circulation or via absorption into the local vasculature. Both compounds gained access to the iris–ciliary body without entry into the anterior cham-

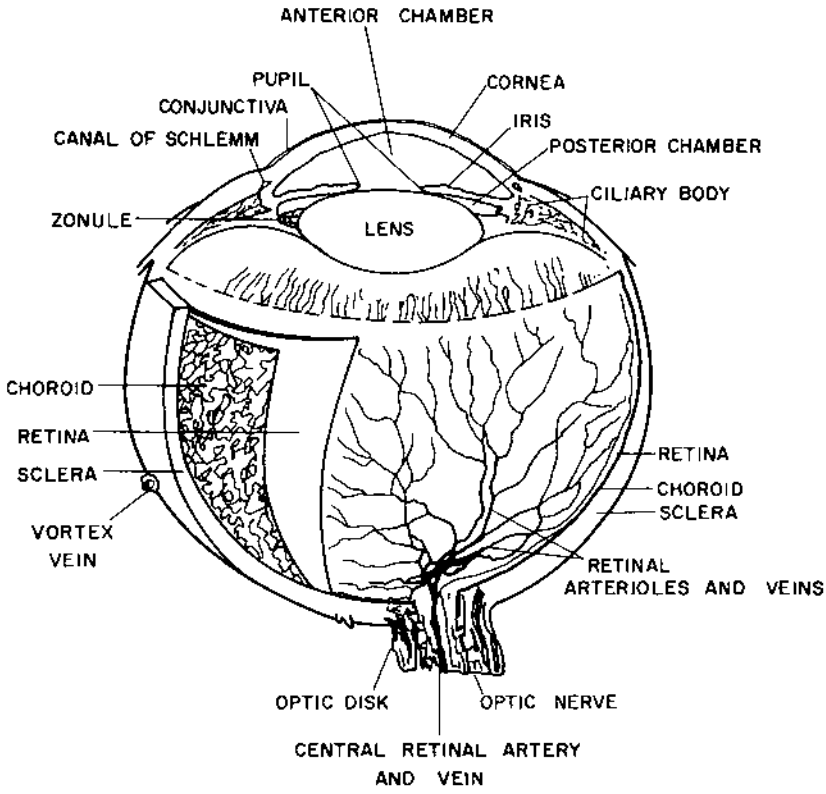


Figure 1 Anatomical structure of the human eye. (From Ref. 12.)

ber. As much as 40% of inulin absorbed into the eye was determined to be the result of noncorneal absorption.

The noncorneal route of absorption may be significant for poorly cornea-permeable drugs; however, corneal absorption represents the major mechanism of absorption for most therapeutic entities. Topical absorption of these agents, then, is considered to be rate limited by the cornea. The anatomical structures of the cornea exert unique differential solubility requirements for drug candidates. Figure 2 illustrates a cross-sectional view of the cornea. In terms of transcorneal flux of drugs, the cornea can be viewed as a trilaminate structure consisting of three major diffusional barriers: epithelium, stroma, and endothelium. The epithelium and endothelium contain on the order of 100-fold the amount of lipid material per unit mass of the stroma (6). Depending on the physiochemical properties of the drug entity, the diffusional resistance offered by these tissues varies greatly (7,8).

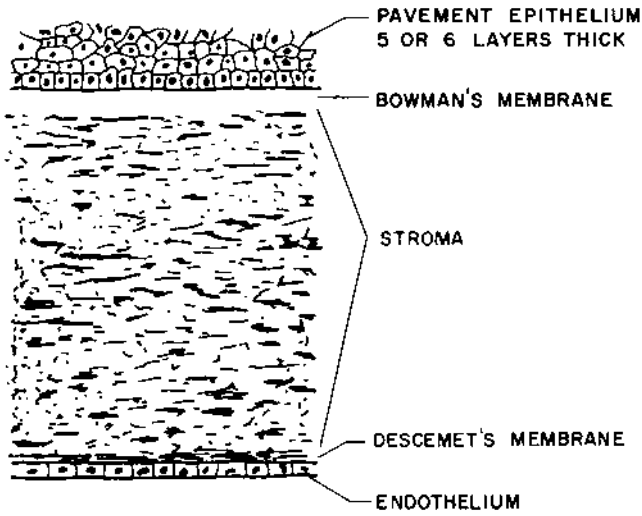


Figure 2 Cross-sectional view of the corneal membrane depicting various barriers to drug absorption. (From Ref. 12.)

The outermost layer, the epithelium, represents the rate-limiting barrier for transcorneal diffusion of most hydrophilic drugs. The epithelium is composed of five to seven cell layers. The basement cells are columnar in nature, allowing for minimal paracellular transport. The epithelial cells, however, narrow distal to Bowman's membrane, forming flattened epithelial cells with zonulae occludentes interjunctional complexes. This cellular arrangement precludes paracellular transport of most ophthalmic drugs and limits lateral movement within the anterior epithelium (9). Corneal surface epithelial intracellular pore size has been estimated to be about 60 Å (10). Small ionic and hydrophilic molecules appear to gain access to the anterior chamber through these pores (11); however, for most drugs, paracellular transport is precluded by the interjectional complexes. In a recent review, Lee (10) discusses an attempt to transiently alter the epithelial integrity at these junctional complexes to improve ocular bioavailability. This approach has, however, only met with moderate success and has the potential to severely compromise the corneal integrity.

Sandwiched between the corneal epithelium and endothelium is the stroma (substantia propia). The stroma constitutes 85–90% of the total corneal mass and is composed of mainly of hydrated collagen (12). The stroma exerts a diffusional barrier to highly lipophilic drugs owing to its hydrophilic nature. There are no tight junction complexes in the stroma, and paracellular transport through this tissue is possible.

The innermost layer of the cornea, separated from the stroma by Descermet's membrane, is the endothelium. The endothelium is lipoidal in nature; however, it does not offer a significant barrier to the transcorneal diffusion of most drugs. Endothelial permeability depends solely on molecular weight and not on the charge of hydrophilic nature of the compound (13,14).

Transcellular transport across the corneal epithelium and stroma is the major mechanism of ocular absorption of topically applied ophthalmic pharmaceuticals. This type of Fickian diffusion is dependent upon many factors, i.e., surface area, diffusivity, the concentration gradient established, and the period over which concentration gradient can be maintained. A parabolic relationship between octanol/water partition coefficient and corneal permeability has been described for many drugs (15–19). The optimal log partition coefficient appears to be in the range of 1–3. The permeability coefficients of 11 steroids were determined by Schoenwald and Ward (15). The permeability versus log partition coefficient fit the typical parabolic relationship, with the optimum log partition coefficient being 2.9. Narurkar and Mitra studied a homologous series of 5′ aliphatic esters of 5-iodo-2′-deoxyuridine (IDU) (16,17). In vitro corneal permeabilities were optimized at a log partition coefficient of 0.88, as can be seen graphically in Figure 3 and in Table 1, where CMP represents the corneal permeability values as measured by in vitro perfusion experiments on rabbit corneas (I = IDU, II = IDU-propionate, III = IDU-butyrate, IV = IDU-isobutyrate,

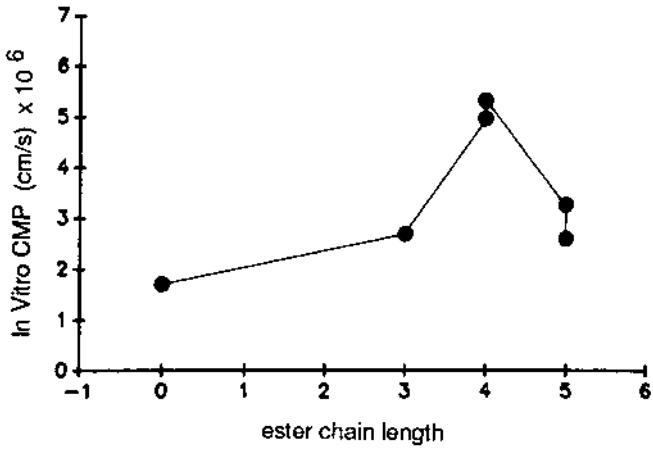


Figure 3 A plot depicting the parabolic relationship between in vitro CMP and ester chain length. (From Ref. 16.)

Table 1 Physicochemical Properties of IDU and Its 5′-Ester Prodrugs

Compound[b]	m.p. (°C)	Solubility[a] in pH 7.4 phosphate buffer, 25°C (M/L ± SD [$\times 10^3$])	K[a] ± SD (octanol/water)
I	168–171 (dec)	5.65 (0.5)	0.11 (0.02)
II	167–168	3.48 (0.3)	4.77 (0.1)
III	145–146	1.45 (0.1)	7.50 (0.3)
IV	144–145	1.75 (0.3)	6.92 (0.8)
V	142–143	0.40 (0.2)	27.54 (2.0)
VI	106–107	0.44 (0.1)	22.10 (1.5)

[a]N = 3.
[b]See text for compound identification.

V = IDU-valerate, VI = IDU-pivalate). A homologous series of *n*-alkyl-*p*-aminobenzoate esters in a study of Mosher and Mikkelson fit the parabolic relationship displaying optimal permeability at a log partition coefficient of 2.5 (18). Maximizing bioavailability of ophthalmic mediations, then, requires that the active compound be neither extremely hydrophilic nor lipophilic. To this end, the pH of the postinstillation precorneal fluid becomes an important factor. The postinstillation pH time course will be dictated by the buffer concentration of the formulation. Most ophthalmic formulations are formulated in the pH range of 5–6; hence, depending on the pK_a of the drug to be administered, the postinstillation buffering capacity of the formulation may greatly affect the drug's bioavailability. Mitra and Mikkelson studied the effect of varying the concentration of citrate buffer in a pH 4.5 formulation on the miosis versus time profile of a 1% pilocarpine solution (20). The area under the miosis-time profile, maximum pupillary response, and duration of mitotic activity were all decreased with increasing buffer concentrations. Figure 4 displays the effect of increasing buffer concentration on the mitosis-time profiles for different total molar citrate values (0.0, 0.055, 0.075, 0.110). The ratio of pilocarpinium ion to pilocarpine increases with the postinstillation buffering capacity, thus reducing the net transcorneal flux of pilocarpine.

III. CONSTRAINTS TO OCULAR DRUG DELIVERY

Ocular tissues are protected from exogenous toxic substances in the environment or bloodstream by a variety of mechanisms, notably, tear secretion continuously flushing its surface, an impermeable surface epithelium, and a

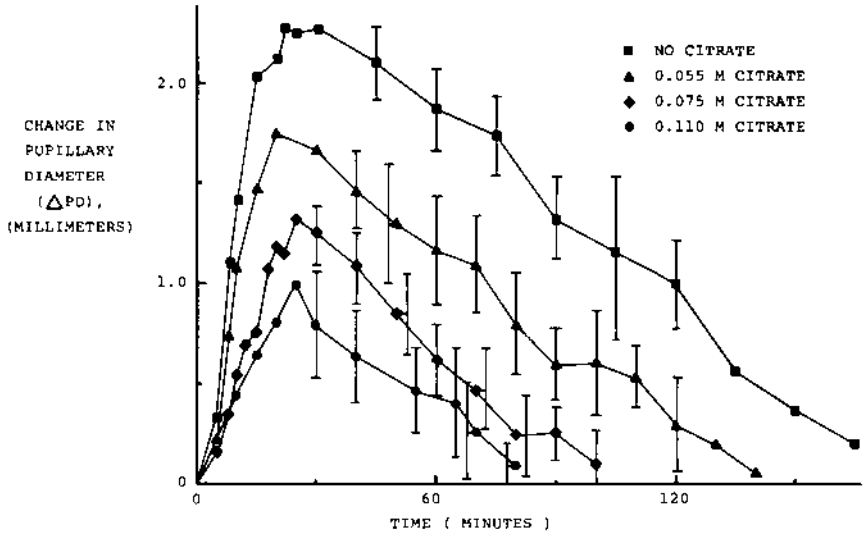


Figure 4 Miosis-time profiles: Plots of the average observed changes in pupillary diameter (ΔPD) as a function of time following the instillation of 25.0 μL of the isotonic 1% pilocarpine nitrate solutions, which contained the different concentrations of citrate buffer. The vertical lines through the data points are ±SD (data points with standard deviation lines omitted is for clarity of the figure). (From Ref. 20.)

transport system actively clearing the retina of agents potentially able to disturb the visual process. However, the same protective mechanisms may cause subtherapeutic drug levels at the intended site. The difficulties can be compounded by the structure of the globe itself, where many of its internal structures are isolated from the blood and the outside surface of the eye. A major goal in ocular therapeutics is to circumvent these structural obstacles and protective mechanisms to elicit desired pharmacological response.

Physiological barriers to the diffusion and productive absorption of topically applied ophthalmic drugs exist in the precorneal and corneal spaces. Anterior chamber factor also greatly influence the disposition of topically applied drugs. Precorneal constraints include solution drainage, lacrimation and tear dilution, tear turnover, and conjunctival absorption. For acceptable bioavailability, a proper duration of contact with the cornea must be maintained. Instilled solution drainage away from the precorneal area has been shown to be the most significant factor reducing this contact

time and ocular bioavailability of topical solution dosage forms (21,22). Instilled dose leaves the precorneal area within 5 minutes of instillation in humans (21,23). The natural tendency of the cul-de-sac is to reduce its fluid volume to 7–10 μL (24–26). A typical ophthalmic dropper delivers 30 μL, most of which is rapidly lost through nasolacrimal drainage immediately following dosage. This drainage mechanism may then cause the drug to be systemically absorbed across the nasal mucosa or the gastrointestinal tract (27). Systemic loss from topically applied drugs also occurs from conjunctival absorption into the local circulation. The conjunctiva possesses a relatively large surface area, making this loss significant.

Simple dilution of instilled drug solution in the tears acts to reduce the transcorneal flux of drug remaining in the cul-de-sac. Lacrimation can be induced by many factors, including the drug entity, the pH, and the tonicity of the dosage from (28–30). Formulation adjuvants can also stimulate tear production (20).

Tear turnover acts to remove drug solution from the conjunctival cul-de-sac. Normal human tear turnover is approximately 16% per minute, which can also be stimulated by various factors, as described elsewhere (21,25). These factors render topical application of ophthalmic solutions to the cul-de-sac extremely inefficient. Typically, less than 1% of the instilled dose reaches the aqueous humor (27,31). The low fraction of applied dose (1%) of drug solution reaching the anterior chamber further undergoes rapid elimination from the intraocular tissues and fluids. Absorbed drug may exit the eye through the canal of Schlemm or via absorption through the ciliary body of suprachoroid into the episcleral space (27). Enzymatic metabolism may account for further loss, which can occur in the precorneal space and/or in the cornea (32,33). Age and genetics have been determined to be two important factors in ocular metabolism (34,35).

Clearly, the physiological barriers to topical corneal absorption are formidable. The result is that the clinician is forced to recommend frequent high doses of drugs to achieve therapeutic effect. This pulsatile dosing not only results in extreme fluctuations in ocular drug concentrations but may cause many local and/or systemic side effects. Approaches taken to circumvent this pulsatile dosing and their ramifications on ocular therapies are the subject matter of this text.

For the effective treatment of diseases involving the retina, drugs must cross the blood-ocular barrier in significant amounts to demonstrate therapeutic effect. The blood-ocular barrier is a combination of microscopic structures within the eye, which physiologically separate it from the rest of the body. It is comprised of two systems: (a) blood-aqueous barrier, which regulates solute exchange between blood and the intraocular fluid, and (b) blood-retinal barrier, which separates the blood from the neural

retina. Both barriers contain epithelial and endothelial components whose tight junctions limit transport.

A transient increase in the blood-retinal barrier permeability can be achieved by modification of the barrier properties. For instance, opening of the blood-retinal barrier can be achieved by intracarotid infusion of a hyperosmotic solution, such as mannitol or arabinose. Perfusion with such a solution for about 30 seconds is shown to open the blood-retinal barrier reversibly. Osmotically induced shrinkage of the retinal and brain capillary endothelial cells causes opening of the tight junctions. Other methods include perfusion with oleic acid or protamine. These methods, however, produce a nonspecific opening of the blood-retinal barrier, possibly with associated retinal and central nervous system toxicity.

Chemical modification is more commonly employed to enhance drug transport across biological barriers. Lipophilic analogs of the parent drug increase lipid solubility and thereby their blood-retinal barrier permeability. Another approach to enhance transport across the blood-retinal barrier could involve utilizing specific carrier systems on the epithelial membrane. Drugs may be modified in such a way that their structures resemble endogenous ligands for a specific carrier system on the blood-retinal barrier.

Drug delivery through nutrient transport systems has been reported previously with intestinal absorption (36–38). β-Lactam antibiotics and other compounds that share the structural features of the endogenous peptides are recognized by the peptide transporters. Recently valacyclovir (valyl ester of acyclovir) (39,40) and valganciclovir (valyl ester of ganciclovir) (41) were shown to be the substrates for peptide transporters. These prodrugs increased the oral bioavailability of acylclovir and ganciclovir significantly (42,43), thus reducing the daily oral dose requirement.

Various transporters/receptors are reported to be present on the retina and/or the blood-ocular barriers. The reader is referred to specific chapters in this volume for detailed description. However, very few studies have been carried out to explore the transporters present on the retina or the blood-ocular barrier. The transporters/receptors present on the retina or the blood-ocular barrier may be exploited to increase ocular bioavailability of drugs with poor intrinsic permeability.

ACKNOWLEDGMENTS

Supported by NIH grants R01 EY09171 and R01 EY10659.

REFERENCES

1. M. Gibaldi and D. Perrier. Pharmacokinetics. New York: Marcel Dekker, 1982.
2. D. M. Maurice. The eye. In: H. Davsoned, ed. Vegetative Physiology and Biochemistry. New York: Academic Press, 1969.
3. I. Ahmed and T. F. Patton. Importance of the noncorneal adsorption route in topical ophthalmic drug delivery. Invest. Ophthalmol. Vis. Sci. 26:584–587, 1985.
4. S. E. Bloomfield, T. Miyata, M. W. Dunn, N. Bueser, K. H. Stenzel, and A. L. Rubin. Soluble gentamicin ophthalmic inserts as a drug delivery system. Arch. Ophthalmol. 96:885–887, 1978.
5. L. Z. Bito and R. A. Baroody. The penetration of exogenous prostaglandin and arachidonic acid into, and their distribution within, the mammalian eye. Curr. Eye Res. 1:659–669, 1981.
6. D. G. Cogan and E. D. Hirch. Cornea: Permeability to weak electrolytes. Arch. Ophthalmol. 32:276, 1944.
7. V. E. Kinsey. Physiology of the eye. In; F. Adler, H., eds. St. Louis: Mosby, 1965.
8. H. S. Huang, R. D. Schoenwald, and J. L. Lach. Corneal penetration behavior of beta-blocking agents II: Assessment of barrier contributions. J. Pharm. Sci. 72:1272–1279, 1983.
9. G. M. Grass and J. R. Robinson. Mechanisms of corneal drug penetration. II: Ultrastructural analysis of potential pathways for drug movement. J. Pharm. Sci. 77:15–23, 1988.
10. V. H. L. Lee. Mechanisms and facilitation of corneal drug penetration, J Controlled Rel, 11:79 (1990).
11. S. D. Klyce and C. E. Crosson. Transport processes across the rabbit corneal epithelium: a review. Curr. Eye Res. 4:323–331, 1985.
12. A. K. Mitra. Ophthalmic drug delivery. In: P. Tyle, ed. Drug Delivery Devices. New York: Marcel Dekker, 1988.
13. A. M. Tonjum. Permeability of rabbit corneal epithelium to horseradish peroxidase after the influence of benzalkonium chloride. Acta Ophthalmol. (Copenh.) 53:335–473, 1975.
14. S. Mishima. Clinical pharmacokinetics of the eye. Proctor lecture. Invest. Ophthalmol. Vis. Sci. 21:504–541, 1981.
15. R. D. Schoenwald and R. L. Ward. Relationship between steroid permeability across excised rabbit cornea and octanol-water partition coefficients. J. Pharm. Sci. 67:786–788, 1978.
16. M. M. Narurkar and A. K. Mitra. Prodrugs of 5-iodo-2′-deoxyuridine for enhanced ocular transport. *Pharm. Res.* 6:887–891, 1989.
17. M. M. Narurkar and A. K. Mitra. Synthesis, physicochemical properties, and cytotoxicity of a series of 5′-ester prodrugs of 5-iodo-2′-deoxyuridine. Pharm. Res. 5:734–737, 1988.