CRC

TRANSDERMAL DELIVERY of DRUGS

Volume I

Agis F. Kydonieus
Bret Berner

CRC PRESS

Transdermal Delivery of Drugs

Volume I

Editors

Agis F. Kydonieus, Ph.D.
President
Hercon Laboratories Corporation
Subsidiary of Health-Chem Corporation
South Plainfield, New Jersey

Bret Berner, Ph.D.
Manager
Pharmaceutical Division
Ciba-Geigy Corporation
Ardsley, New York

CRC Press, Inc.
Boca Raton, Florida

Library of Congress Cataloging-in-Publication Data

Transdermal delivery of drugs.

Includes bibliographies and index.
1. Ointments. 2. Skin absorption. 3. Drugs--Controlled release. I. Kydonieus, Agis F., 1938- II. Berner, Bret. [DNLM: 1. Administration, Topical. 2. Delayed-Action Preparations. 3. Drugs--administration & dosage. 4. Skin Absorption. WB 340 T7723]
RS201.03T7255 1987 615'.67 86-2585
ISBN 0-8493-6483-3 (set)
ISBN 0-8493-6484-1 (v. 1)
ISBN 0-8493-6485-X (v. 2)
ISBN 0-8493-6486-8 (v. 3)

Direct all inquiries to CRC Press, Inc., 2000 Corporate Blvd., N.W., Boca Raton, Florida, 33431.

International Standard Book Number 0-8493-6483-3 (set)
International Standard Book Number 0-8493-6484-1 (v. 1)
International Standard Book Number 0-8493-6485-X (v. 2)
International Standard Book Number 0-8493-6486-8 (v. 3)

Library of Congress Card Number 86-2585
Printed in the United States

PREFACE

The introduction of the first transdermal patch containing scopolamine brought about a tremendous interest in the usage of intact skin as a portal of entry of drugs into the systemic circulation of the body. Several transdermal products followed into the marketplace, in particular, devices containing nitroglycerin, clonidine, isosorbide dinitrate (Japan), and estradiol (Switzerland). Some two dozen drugs are now in different steps of transdermal product development. A plethora of transdermal development departments and companies have emerged. While the potential advantages of transdermal delivery such as (1) avoidance of hepatic "first-pass" metabolism, (2) maintenance of steady-state plasma levels of drug, and (3) convenience of dosing were readily identified, the limitations of the barrier and immune properties of skin are only now being defined. Continued technological advances are requiring either circumventing these responses of the skin or adroit identification of conditions in search of controlled-release therapies. The goals of these volumes are to collect the current knowledge to further research in transdermal delivery and to serve as an introduction to the novice.

The series of volumes is divided into four main sections pertaining to Methodology, The Transdermal Device, The Skin, and The Drug. For the recent practitioner in the field, an overview section has been included to provide a background about the controlled release devices, the diffusion of drugs through polymers, and the anatomy and biochemistry of skin.

In the methodology section, the techniques used to determine in vitro and in vivo skin permeation are presented. The special considerations concerning animal and human experimentation are described including in vivo methodology, skin condition, and individual variations.

A section on transdermal devices concludes the first volume. Here we asked scientists from six companies to discuss briefly their transdermal technology and product development areas.

The volume on skin contains chapters on the parameters affecting skin penetration, including a chapter on aging, pharmacokinetics of transdermal delivery, models for predicting the permeability of drugs through skin from the physicochemical parameters of the drug, the correlations among human skin, reconstituted skin, artificial membranes, and the potential of increasing skin permeability by the use of chemical enhancers or vehicles. Finally, a chapter on the crucial area of cutaneous toxicology describes contact dermatitis and microorganism growth and infections.

In the third volume, the drug parameters important to transdermal delivery are discussed. The thermodynamics governing transdermal delivery and models and typical approaches for prodrugs are also presented. Finally, a literature review of the permeability of drugs through the skin is presented. This compilation of existing skin permeation data should serve as a useful reference tool.

Obviously, in this rapidly expanding field, several important omissions must have occurred despite our effort to include significant developments known by 1984, when most of the manuscripts were collected. Nevertheless, we hope this effort will prove to be of value to scientists and product development engineers seeking up-to-date information in this area.

We are indebted to the authors for their cooperation in adhering to manuscript specifications and to Mrs. Robin Tyminski for her efforts in typing and assisting in the editorial endeavors. Finally, we would like to thank the management of Health-Chem Corporation, the parent of Hercon Laboratories, who have been strong advocates of controlled release for many years and have given the editors all the support required to complete this undertaking.

Agis F. Kydonieus
Bret Berner

THE EDITORS

Agis F. Kydonieus, Ph.D., is President of Hercon Laboratories Corporation, a subsidiary of Health-Chem Corporation, New York. Dr. Kydonieus graduated from the University of Florida in 1959 with a B.S. degree in Chemical Engineering (summa cum laude) and received his Ph.D. from the same school in 1964.

Dr. Kydonieus is a founder of the Controlled Release Society and has served as a member of the Board of Governors, Program Chairman, Vice President, and President. He is presently a trustee of the Society. He is also founder of Krikos, an international Hellenic association of scientists, and has served a treasurer and a member of its Board of Directors. He is also a member of the editorial board of the *Journal of Controlled Release,* and a member of many societies including the American Association of Pharmaceutical Scientists, American Institute of Chemical Engineers, and the Society of Plastics Engineers.

Dr. Kydonieus is the author of over 125 patents, publications, and presentations in the field of controlled release and biomedical devices. He is the Editor of *Controlled Release Technologies* and *Insect Suppression with Controlled Release Pheromone Systems,* both published with CRC Press.

Bret Berner, Ph.D., is Manager of Basic Pharmaceutics Research for CIBA-GEIGY, Inc. Dr. Berner received his B.A. degree from the University of Rochester in 1973 and his Ph.D. from the University of California at Los Angeles in 1978. Before joining CIBA-GEIGY in 1985, he was Director of Research, Hercon Division of Health-Chem Corporation. Dr. Berner also held the position of staff scientist with Proctor & Gamble, Co. following his graduation from UCLA.

Dr. Berner's current research directs novel drug delivery research groups including transdermal, gastrointestinal, and other delivery routes, polymer systems, pharmacokinetics, pharmacodynamics, and analytical chemistry.

CONTRIBUTORS

Bret Berner, Ph.D.
Manager
Pharmaceuticals Division
Ciba-Geigy Corporation
Ardsley, New York

Donald Bissett, Ph.D.
Proctor & Gamble Company
Miami Valley Laboratories
Cincinnati, Ohio

Yie W. Chien, Ph.D.
Professor and Chairman
Department of Pharmaceutics
Rutgers University
Piscataway, New Jersey

Gary W. Cleary, Ph.D.
President
Cygnus Research Corporation
San Mateo, California

Gordon L. Flynn, Ph.D.
Professor of Pharmaceutics
College of Pharmacy
University of Michigan
Ann Arbor, Michigan

Robert M. Gales, M.S.
Senior Product Development Manager
Product Development Area
Alza Corporation
Palo Alto, California

Timothy A. Hagen
College of Pharmacy
University of Michigan
Ann Arbor, Michigan

Dean S.T. Hsieh, Ph.D.
President
Conrex Pharmaceutical Corporation
Edison, New Jersey

Allan Hymes, Ph.D.
Medical Consultant
LecTec Corporation
Minneapolis, Minnesota

Aziz Karim, Ph.D.
Director
Department of Pharmacokinetics
G.D. Searle & Company
Skokie, Illinois

Alec D. Keith, Ph.D.
Professor
Department of Biophysics
Pennsylvania State Univeristy
University Park, Pennsylvania

Agis F. Kydonieus, Ph.D.
President
Hercon Laboratories Corporation
Subsidiary of Health-Chem
Corporation
New York, New York

Howard Maibach, M.D.
Professor
Department of Dermatology
University of California
at San Francisco
San Francisco, California

Arthur S. Obermayer, Ph.D.
Chairman of the Board
Moleculon, Inc.
Cambridge, Massachusetts

Nikolaos A. Peppas, Sc.D.
Professor
School of Chemical Engineering
Purdue University
West Lafayette, Indiana

Marilou Powers Cramer, B.S.
Director of Clinical Sciences
Alza Corporation
Palo Alto, California

David Rolf, Ph.D.
Director of Medical Services
LecTec Corporation
Minneapolis, Minnesota

Jane E. Shaw, Ph.D.
President
Alza Corporation
Palo Alto, California

Ward M. Smith
College of Pharmacy
University of Michigan
Ann Arbor, Michigan

Ronald C. Wester, Ph.D.
Assistant Research Dermatologist
Department of Dermatology
University of California
at San Francisco
San Francisco, California

TABLE OF CONTENTS

Volume I

Section I: Overview

Chapter 1

FUNDAMENTALS OF TRANSDERMAL DRUG DELIVERY

Agis F. Kydonieus

TABLE OF CONTENTS

I. INTRODUCTION

Controlled release may be defined as a technique or method in which active chemicals are made available to a specified target at a rate and duration designed to accomplish an intended effect. A definition perhaps more acceptable to the chemist and engineer may be the permeation-moderated transfer of an active material from a reservoir to a target surface to maintain a predetermined concentration or emission level for a specified period of time. Transdermal drug delivery can, therefore, be defined as the controlled release of drugs through intact skin.

In this book we will further limit the definition of transdermal systems to the newly introduced polymeric devices designed for prolonged delivery of drug through intact skin.

II. RATIONALE FOR TRANSDERMAL CONTROLLED RELEASE MEDICATION

During the last decade, controlled release technology has received increasing attention in the face of a growing awareness that substances ranging from drugs to agricultural chemicals are frequently excessively toxic and sometimes ineffective when administered or applied by conventional means. Thus, conventionally administered drugs in the form of pills, capsules, injectables, and ointments are introduced into the body as pulses that usually produce large fluctuations of drug concentrations in the bloodstream and tissues and consequently, unfavorable patterns of efficacy and toxicity.

The process of molecular diffusion through polymers and synthetic membranes has been used as an effective and reliable means of attaining transdermal controlled release of drugs and pharmacologically active agents. Central to the development of transdermal controlled delivery systems is the synthesis of the principles of molecular transport in polymeric materials and those of pharmacokinetics and pharmacodynamics. In transdermal drug delivery, pharmacokinetics is an important consideration because target tissues are seldom directly accessible, and drugs must be transported from the portal of entry on the body through a variety of biological interfaces to reach the desired receptor site. During this transport process, the drug can undergo severe biochemical degradation and, thereby, produce a delivery pattern at the receptor site that differs markedly from the pattern of drug release into the system.

A. Conventional Delivery vs. Transdermal Controlled Release of Medication

Conventionally, active agents are most often administered to a system by nonspecific, periodic applications. For example, in medical treatment, drugs are introduced at intervals by ingestion of pills or liquids or by injection. The drugs then circulate throughout much of the body, and the concentration of the active agent rises to high levels, system-wide, at least initially.[1] Both by injection and orally, the initially high concentrations may be toxic and cause side effects both to the target organ and neighboring structures. As time passes, the concentration diminishes, owing to natural metabolic processes, and a second dose must be administered to prevent the concentration from dropping below the minimum effective level. Such responses are shown in Figure 1. This situation is, of course, very inconvenient and difficult to monitor, and careful calculations of the amount of residual active agent must be made to avoid overdosing. The close attention required, together with the fact that large amounts of the drug are lost in the vicinity of the target organ, make this type of delivery inefficient and costly. In addition, side effects owing to drugs misdirected to nontarget tissues are also possible.

Cowsar has discussed a hypothetical drug that is effective at 5 ± 2 mg/kg (below 3 mg/kg ineffective, above 7 mg/kg toxic) and has a half-life in vivo of 8 hr; his regimen calls

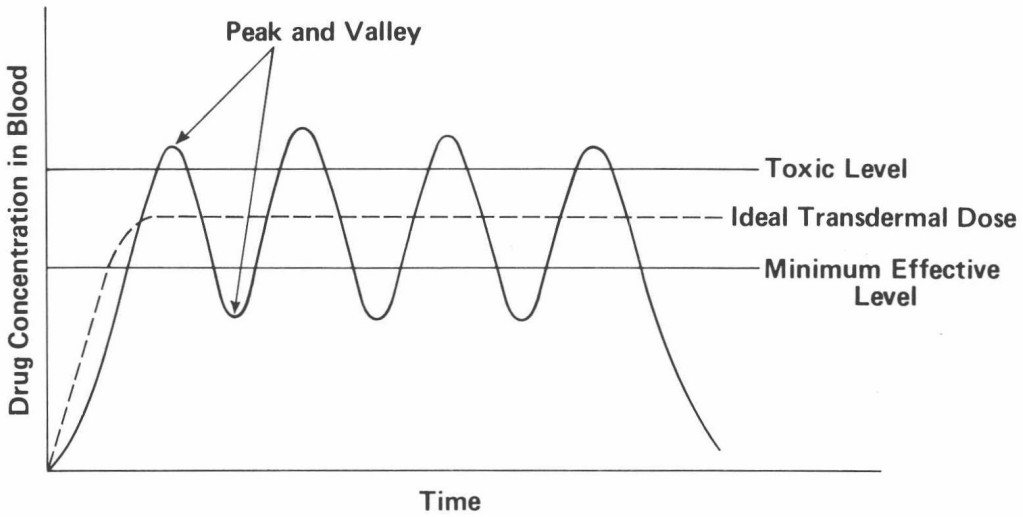

FIGURE 1. Hypothetical blood level pattern from a conventional multiple dosing schedule, and the idealized pattern from a transdermal controlled release system.

Table 1
SOME ADVANTAGES OF TRANSDERMAL MEDICATION

Bypass hepatic "first pass" and gastrointestinal incompatibility
Reduce side effects due to the optimization of the blood concentration-time profile
Provide predictable and extended duration of activity
Greater patient compliance due to the elimination of multiple dosing schedules
Enhance therapeutic efficacy
Reduce frequency of dosage
Reversibility of drug delivery which would allow for removal of the drug source
Minimize inter- and intrapatient variation
Self administration

for the patient to be treated for 10 to 14 days.[2] He found that an initial injection of 7 mg/kg followed by 32 subsequent injections of 5 mg/kg at 10-hr intervals was required. If 14-mg/kg injections were given to reduce the number of injections needed, an effective level could be maintained, but for 8 hr, the concentration of the drug was at a potentially toxic level. If a transdermal controlled release product were available, a single administration providing the 5 mg/kg would be needed.

In Figure 1, the ideal transdermal controlled release rate is illustrated, i.e., a constant concentration, one that is effective but not toxic, is maintained for the desired time. Advantages of this system for therapeutic agents are (1) reproducible and prolonged constant delivery rate, (2) convenience of less frequent administrations, and (3) reduced side effects because the dose does not exceed the toxic level.

B. Advantages and Limitations

1. Advantages

The advantages of transdermal medication indicated above are indeed great. However, transdermal systems can impart other important advantages to active agents that could be sufficient to elevate many products to commercial successes. Table 1 lists a number of these successes, the most important of which are discussed later.

Table 2
RESEARCH EXPENDITURE AND DEVELOPMENT PRODUCTIVITY IN U.S. PHARMACEUTICAL INDUSTRY[3]

	1960	1965	1975
Research expenditure (in million dollars)	200	351	1028
Development productivity (number of new drug entities successfully developed and marketed)	50	25	15
Research & Development effectiveness:			
Cost (million dollars/new drug entity)	2	14	68
Time (years)	2	—	10—15

From Katz, M., *Drug Cosmet. Ind.*, 40, 1980. With permission.

Table 3
THE BIRTH PANGS OF A NEW DRUG[3] (U.S. PHARMACEUTICAL INDUSTRY IN 1970)

	Drug substances
Results from extraction, isolation and synthesis for therapeutic purposes	126,060 (100%)
Submission for pharmacology testing	703,900 (558%)
Selection for clinical testing	1,013 (0.8%)
NDA approval	16 (0.013%)

From Katz, M., *Drug Cosmet. Ind.*, 40, 1980. With permission.

a. Economic Considerations

The cost of developing new drug entities as well as the time it takes to bring such drugs to the marketplace has been continuously increasing, as shown in Table 2.

Thus, in 1975 over one billion dollars was spent in pharmaceutical research and it took an average of 10 to 15 years and over 60 million dollars to bring a new drug to the market.[3] As it is shown in Table 2 in 1960, it took only 2 years to bring a new drug to the marketplace with a research effort of less than 2 million dollars.

Even more startling are the data shown on Table 3 which indicate that while 126,000 drug substances were investigated in 1970, only 16 were approved by the FDA for use on humans that same year; pharmacological and clinical testing and undoubtedly marketing considerations eliminated all other.

In transdermal delivery you may start with a drug that is already approved, therefore, the risks, time to the marketplace, and the research costs are all substantially reduced. These costs will vary from organization to organization but should not exceed 4 million dollars and 4 years.

b. Clinical Improvements

Transdermal delivery can increase the therapeutic value of many drugs by obviating specific problems associated with the drug. Such problems might include, gastrointestinal irritation, low absorption, decomposition due to hepatic "first pass" effect, formation of metabolites that cause side effects, and short half-life necessitating frequent dosing. In transdermal medication, the above problems can be eliminated because the drug diffuses over a prolonged period of time directly into the bloodstream. An excellent example is that of nitroglycerin used in angina pectoris patients as a vasodilator. Nitroglycerin has a 90% hepatic "first pass" effect, so it could not be used orally to prevent angina pectoris attacks. Its main use was as a sublingual pill to abort an attack after it occurred. With the advent

of transdermal medication, nitroglycerin is now used as a patch to prevent angina pectoris attacks.

A gold mine might exist in the files of major drug companies in drug substances discarded because of gastrointestinal irritation, low absorption, or other specific problems which can be bypassed by the use of transdermal medication.

2. Limitations

Though the advantages of transdermal medication are impressive, the merits of each application have to be examined individually, and the positive and negative effects weighed carefully before large expenditures for developmental work are committed.

Only a small percentage of the drugs can be delivered transdermally due to three limitations, difficulty of permeation through human skin, skin irritation, and clinical need.

In addition to its use as a physical barrier, the human skin functions as a chemical barrier as well. The outermost layer of the skin, the stratum corneum, is an excellent barrier to almost all chemicals including drugs. The anatomy and biochemistry of skin are discussed in Chapter 3. Thus, if the drug dosage required for therapeutic value is more than 10 mg per day, the delivery transdermally will be very difficult if not impossible. Daily dosages of less than 5 mg are preferred.

Skin irritation or contact dermatitis of excipients and enhancers of the drug used to increase percutaneous absorption is another major limitation. Contact irritant dermatitis results from direct toxic injury to cell membranes, cytoplasms, or nuclei. Contact allergic dermatitis involves host immunological activity. Cutaneous toxicology and testing methodology are discussed in Chapter 13.

Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product. Oral medication is adequate for the delivery of most drugs. However, with the recent FDA approval of a 7-day clonidine patch, the clinical need might come in the form of convenience and greater patient compliance due to the elimination of multiple dosing schedules.

III. SYSTEMS FOR TRANSDERMAL DELIVERY OF MEDICATION

The major parts of a transdermal system are

1. A controlled release device comprised of polymers, the drug, excipients, and enhancers.
2. A fastening system, usually a pressure sensitive adhesive, for adhering the device to the skins.
3. A hermetically sealed package composed of impervious films.

A. Brief Description of Controlled Release Devices

Table 4 categorizes the various controlled release technologies including physical as well as chemical systems.[4] The chemical systems do not appear to be useful for the delivery of drugs transdermally. The four major classes of physical systems are described below.

1. Reservoir Devices with Rate-Controlling Membrane

These include microcapsules, macrocapsules, and membrane systems. Membrane systems are most applicable in transdermal delivery and are composed of a liquid containing the drug encapsulated by a solid or microporous polymeric membrane. Such systems are discussed in Volume II, Chapter 5.

2. Reservoir Devices without Rate-Controlling Membrane

These systems include hollow fibers, impregnation in porous plastics such as MPS® porous

Table 4
CATEGORIZATION OF POLYMERIC SYSTEMS FOR CONTROLLED RELEASE

- Physical systems
  - Reservoir systems with rate-controlling membrane
    - Microencapsulation
    - Macroencapsulation
    - Membrane systems
  - Reservoir systems without rate-controlling membrane
    - Hollow fibers
    - Poroplastic® and Sustrelle® ultramicroporous cellulose triacetate
    - Porous polymeric substrates and foams
  - Monolithic systems
    - Physically dissolved in nonporous, polymeric, or elastomeric matrix
      - Nonerodible
      - Erodible
      - Environmental agent ingression
      - Degradable
    - Physically dispersed in nonporous, polymeric, or elastromeric matrix
      - Nonerodible
      - Erodible
      - Environmental agent ingression
      - Degradable
  - Laminated structures
    - Reservoir layer chemically similar to outer control layers
    - Reservoir layer chemically dissimilar to outer control layers
  - Other physical methods
    - Osmotic pumps
    - Adsorption onto ion-exchange resins
- Chemical systems
  - Chemical erosion of polymer matrix
    - Heterogeneous
    - Homogeneous
  - Biological erosion of polymer matrix
    - Heterogeneous
    - Homogeneous

PVC sheet, Millipore® filters, and Celgard® porous polypropylene, foams, and possibly hydrogels and ultramicroporous cellulose triacetate.

The simplest example is perhaps the hollow fibers which hold the active agent in their bore and release it by diffusion through the air layer above the agent. Systems utilizing impregnated porous plastics (PVC and Celgard®, etc.) are more complex, but in all cases, the active agent is retained by capillary action physically imbedded in the pores. Release also occurs by diffusion through the air layer above the liquid that fills the pores. Strictly speaking, most of these systems may be considered monolithic matrix systems, except that interaction of active agent and polymer is minimal. Transdermal devices using ultramicroporous cellulose triacetate are discussed in Volume III, Chapter 4.

3. Monolithic Systems

Probably the simplest and least expensive way to control the release of a drug is to disperse it in an inert polymeric matrix. In monolithic systems, the active agent is physically blended with the polymer powder and then fused together by compression molding, injection molding, screw extrusion, calendering, or casting,[5] all of which are common processes in the plastics industry.

Similarly, the active agent can be blended with elastomeric materials in the mixing step like any of the other additives, e.g., accelerators, reinforcing pigments, stabilizers, and processing aids.[6]