CRC

TRANSDERMAL DELIVERY *of* DRUGS

Volume III

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CRC PRESS

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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.

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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.

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Chapter 1

DRUG PARAMETERS IMPORTANT FOR TRANSDERMAL DELIVERY

Richard H. Guy and Jonathan Hadgraft

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I. INTRODUCTION

Transdermal drug delivery to achieve systemic pharmacological effect is now recognized as a viable means to administer therapeutic agents. Devices have been described for the delivery of such diverse molecules as scopolamine,[1] nitroglycerin,[2-4] clonidine,[5] and estradiol.[6] However, the range of chemical types encompassed by these drugs should not lead one to assume that transdermal delivery will be successful for all species. Indeed, there are important limitations upon the properties of the agent to be delivered such that many drugs in common use are precluded from this mode of administration. It is the purpose of this chapter to identify the drug criteria which determine the feasibility of transdermal delivery. We have chosen to consider the relevant drug parameters in three categories:

1. Biological
2. Physicochemical
3. Pharmacokinetic

We shall address each of these in turn and conclude by providing examples for which the various contributory factors come together to predict the possible success of the transdermal delivery route.

II. BIOLOGICAL CRITERIA

A. Therapeutic Index (TI)

With respect to the TI of the drug, the classic controlled delivery figure (Figure 1) encapsulates the required criteria for transdermal input. Administration must lead to plasma levels (or, more specifically, drug concentrations in the "biophase") above the minimum effective concentration (MEC) but below the minimum toxic concentration (MTC). The sustained delivery should produce steady levels of circulating drug and overcome, thereby, the "sawtooth" profile produced by more conventional dosing regimens, e.g., multiple oral doses. In this way, one may maintain the drug concentration within the TI, minimize the occurrence of side effects, and improve patient compliance.

As we shall see, however, for transdermal drug delivery, the therapeutic agent must be potent if the administration route is to be a feasible option. To date, the excellent barrier properties of the stratum corneum have limited the drugs chosen for transdermal delivery to those whose daily dose requirements are on the order of mg/day. In the majority of cases, this translates into a plasma concentration of approximately ng/mℓ. It remains to be seen whether, with the use of penetration enhancers, for example, the biophase level of active agent can be increased further without resorting to an unacceptable surface area of contact between skin and device. More discussion and illustration of these points is presented later in this chapter.

B. Drug Inactivation

A frequently cited advantage of transdermal input is the ability to avoid inactivation of the drug through a hepatic first-pass effect or by GI degradation. This observation is perhaps best exemplified by nitroglycerin (NTG) which is not only subject to major metabolic clearance by the liver but is also decomposed by circulating red blood cells.[7,8]

C. Biological Half-Life ($t_{1/2}$)

The $t_{1/2}$ criterion for drugs administered transcutaneously is that which characterizes all forms of sustained or prolonged delivery; namely, that the half-life be short rather than long. If the $t_{1/2}$ is large then, because percutaneous absorption is, on the whole, a slow process,

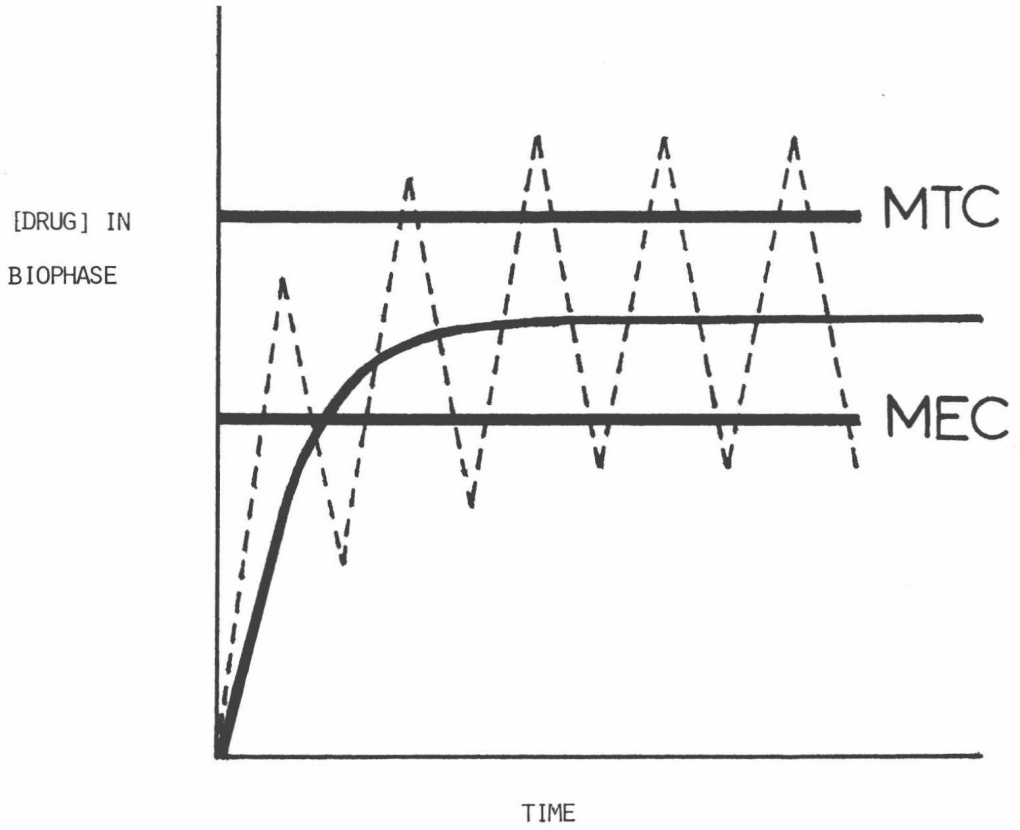

FIGURE 1. The classic goal of controlled drug input: the rapid attainment of a steady prolonged biophase level within the therapeutic index. The profile is contrasted with that resulting from multiple doses of a "conventional" formulation (leading to the "sawtooth" pattern and periods of both over- and underdosing).

the attainment of steady-state plasma levels will be delayed considerably. We may illustrate this point using in vivo transdermal delivery data for NTG and clonidine.[9,10] Plasma levels following administration of these two drugs to human volunteers are shown in Figure 2. In both studies, the results of which are combined on this figure, drug was delivered from a "membrane-controlled" patch of similar design. It is immediately apparent that steady-state levels of NTG ($t_{1/2} \simeq 2$ min[11]) are achieved much more rapidly than those of clonidine ($t_{1/2} \simeq 10$ hr[11]). Although there are physicochemical factors which also influence the time to steady state in these situations, none is capable of exerting such a dramatic effect as the $t_{1/2}$.

D. Limiting Factors

Finally, in this section, it is appropriate to highlight three potential biological limitations to transdermal drug delivery.

1. The administered drug must not induce a cutaneous irritant or allergic response.
2. Because the barrier nature of skin ensures that transdermal input provides rather constant delivery of drug, it is important that the pharmacological effect of the agent be suited to this absorption behavior. In other words, one must be careful to ascertain that tolerance to the drug does not develop under the near zero-order profile of transdermal delivery.
3. Cutaneous metabolism remains an essentially unknown variable in topical drug delivery. The skin does contain multiple enzyme systems many of which are capable of

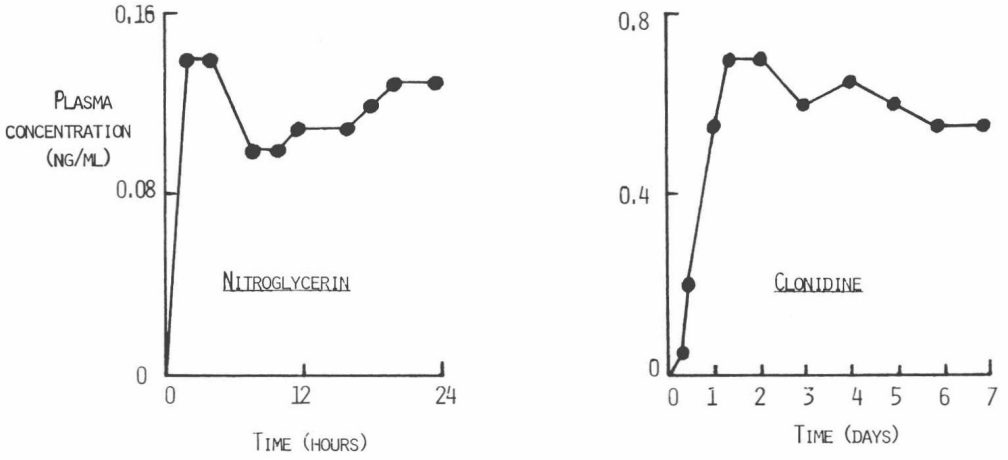

FIGURE 2. In vivo plasma concentration vs. time data for NTG and clonidine following transdermal delivery.[9,10] The difference in rates of attainment of steady-state blood levels reflects primarily the difference in the biological half-lives of the two drugs.

converting transporting drug molecules to metabolite species.[12] Thus, the possibility of a significant cutaneous first-pass effect exists. Experimental determinations of the simultaneous transport and bioconversion of penetrating molecules are sparse and inconclusive as to the potential importance of cutaneous metabolism; in particular, unambiguous in vivo demonstration of the phenomenon is difficult. With respect to transdermal drug delivery, a recent study of NTG absorption in rhesus monkeys[13] offers the most relevant evidence. In this investigation, it was concluded that a skin first-pass effect of 15 to 20% could be inferred from the results. If such an effect proves to be more generally true, then we may expect a considerable amount of activity in this research area during the next few years. Elsewhere, in connection with topical drug administration, in vitro studies have shown that excised skin remains enzymatically viable.[14-16] The possible ramifications of these observations have also been subjected to theoretical treatment;[17-20] the implications of this work are considerable and await experimental test. Parenthetically, one should add that bacteria are present on the skin surface and that these microflora are possible inactivators of transdermally delivered drugs. The occlusive environment beneath a therapeutic system may present an attractive region for this interaction.

III. PHYSICOCHEMICAL CRITERIA

In asking the question, "what physicochemical criteria determine the feasibility of delivering a drug transdermally", it is instructive to identify the sequential physical processes which a drug, presented in a topical delivery system, must undergo to become available in the systemic circulation. These events may be summarized as follows:

1. Drug transport within the delivery system to the device-skin surface interface
2. Partitioning of drug from the delivery system into the stratum corneum
3. Diffusion of drug across the stratum corneum
4. Drug partitioning from the stratum corneum into the viable epidermis.
5. Transport of drug through the viable tissue
6. Drug uptake by the cutaneous microcapillary network and subsequent systemic distribution.

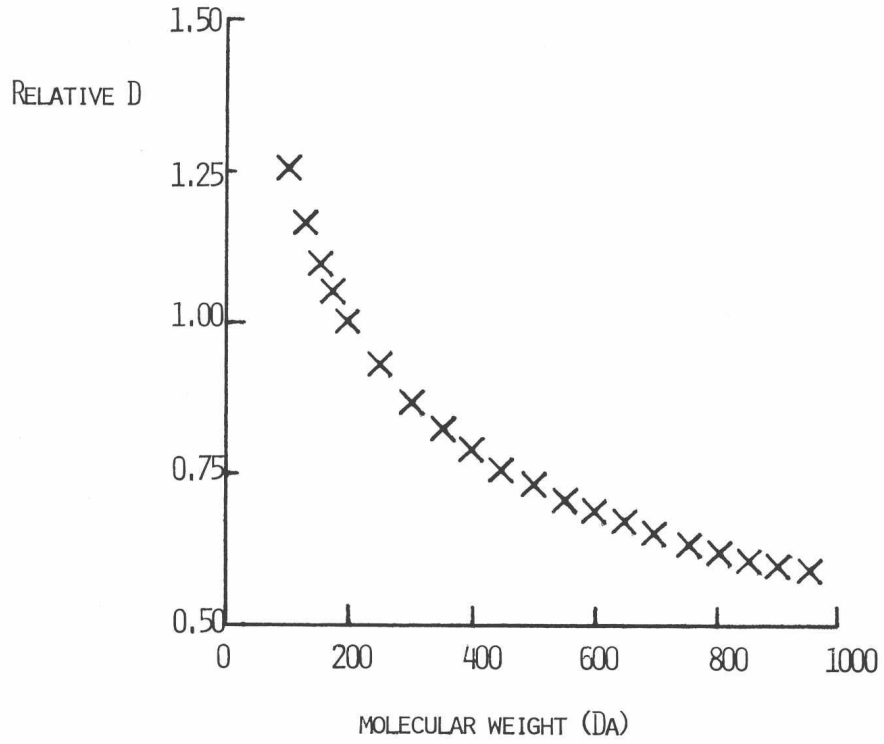

FIGURE 3. Idealized dependence of solute diffusion coefficient (D) upon molecular weight (M) according to Equation 1. The ordinate expresses a relative D, normalized with respect to that of a molecule of molecular weight 200 daltons.

The key words, which are pertinent to this stage of the discussion, therefore, are diffusion and partitioning.

A. Diffusion

The transport characteristics of the drug are determined primarily by its size and by its level of interaction with the media through which diffusion is taking place, i.e., delivery system, stratum corneum, viable epidermis. Most drugs in current use have molecular weights of less than 1000 daltons. Beyond this magnitude, organic molecules tend to fall into categories such as polymers or peptides, for which, we shall see, there are overriding factors that control penetration. For the smaller species ($<$ 1000 daltons), the effect of size on diffusion in liquids may be viewed in terms of the Stokes-Einstein equation, that is

$$D = C \cdot M^{-1/3} \quad (1)$$

where M is molecular weight and C is a constant. Although this is an ideal equation which makes the assumption that the molecules are spherical, it does provide a reasonable estimate of the size effect on diffusion. It also implies that the molecular weight plays a rather minor role in influencing D, i.e., the $M^{-1/3}$ function is not very powerful; see Figure 3.

However, it is clear from the literature[21] that the diffusion coefficient of chemicals through the skin, e.g., the stratum corneum, is very sensitive to the nature of the penetrant, in specific to the degree of interaction between the molecule and the tissue. Scheuplein and Blank,[22] for example, have quoted values of D (for stratum corneum transport) ranging from 10^{-13} to 10^{-9} cm^2/sec. The diffusion coefficients were inferred from permeability data through excised skin and the substances studied encompassed a range which included water,

Table 1
IN VITRO SKIN PERMEABILITY COEFFICIENTS (P) OF TWO HOMOLOGOUS GROUPS OF STEROIDS

Steroid	Hydroxyl groups	Carbonyl groups	10^6P/cm/hr
Progesterone	0	2	1500
Hydroxyprogesterone	1	2	600
Cortexone	1	2	450
Cortexolone	2	2	75
Cortisone	2	3	10
Cortisol	3	2	3
Estrone	1	1	3600
Estradiol	2	0	300
Estriol	3	0	40

simple alcohols, and a number of steroids. The evaluation of D from the experimental data required the assumption of a specific diffusion path length through the stratum corneum; thus, while the absolute magnitudes of the D values quoted may not be precise, the span of the data, i.e., D varying over four orders of magnitude, is representative. Of course, one must realize that the experimental observation is an *apparent* diffusion coefficient which contains information about the degree of interaction or binding between the penetrant and skin. Seemingly minor changes in chemical structure, therefore, can lead to dramatic alterations in permeation behavior, for example, Scheuplein et al. demonstrated an enormous range of permeability coefficients for a closely related series of steroidal molecules[23] (see Table 1). It seems clear that the introduction of increasing polarity into a molecular backbone leads to significant dimunition in skin penetration capability.

B. Partitioning

Among the six sequential steps in percutaneous absorption identified above, there are two key partitioning processes, between the delivery system and the stratum corneum and between the lipophilic stratum corneum and the much more aqueous in nature viable epidermis.

Hence, the partitioning criteria demanded of a drug candidate for transdermal delivery are severe. First, the molecule must favor the stratum corneum over the device and then, the relative affinity of the drug for stratum corneum and viable tissue must be reasonably balanced (to ensure adequate throughput of material into the systemic circulation). Thus, extreme partitioning characteristics are not conducive to successful drug delivery via the skin.

Although it is inappropriate here to review comprehensively the literature pertaining to drug penetration as a function of partition coefficient, it is instructive to consider a few illustrations of such work. Human skin absorption has been correlated with a heptane-aqueous buffer partition coefficient (K).[24] Agreement was reasonable for the most oil-soluble and the most water-soluble penetrants but the intermediate range of compounds were not differentiated in any consistent fashion. The permeability of human epidermis to phenolic compounds in vitro has been measured.[25] Penetration could be related to the substrate K(octanol/water) provided that the applied concentration of phenol did not damage the cutaneous barrier. Steroid penetration in man has been studied[26] and a reasonable coincidence was found between estimated half-lives for penetration and benzene solubility. A linear free energy relationship between the bioresponse and the physical chemical quantity was calculated. Lien and Tong[27] have also used the extrathermodynamic approach to establish linear