

In Vitro Percutaneous Absorption: Principles, Fundamentals, and Applications

Editors

Robert L. Bronaugh, Ph.D.

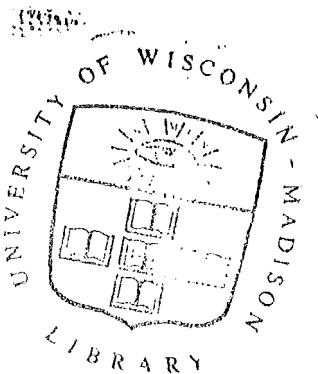
Supervisory Research Pharmacologist
Division of Toxicological Studies
U.S. Food and Drug Administration
Washington, D.C.

Howard I. Maibach, M.D.

Professor of Dermatology
School of Medicine
University of California
San Francisco, California



CRC Press
Boca Raton Ann Arbor Boston London



Library of Congress Cataloging-in-Publication Data

In vitro percutaneous absorption : principles, fundamentals, and applications / editors, Robert L. Bronaugh, Howard I. Maibach.

p. cm

Includes bibliographical references.

Includes index.

ISBN 0-8493-4748-3

1. Skin absorption.
2. Skin absorption--Research--Methodology.
3. Skin--Cultures and culture media. I. Bronaugh, Robert L., 1942-II. Maibach, Howard I.

[DNLM: 1. Administration, Cutaneous. 2. Models, Biological.

3. Skin--metabolism. 4. Skin Absorption--physiology. WR 102 135]

QP88.5.I46 1991

612.7'91--dc20

DNLM/DLC

for Library of Congress

90-15183

CIP

This book represents information obtained from authentic and highly regarded sources. Reprinted material is quoted with permission, and sources are indicated. A wide variety of references are listed. Every reasonable effort has been made to give reliable data and information, but the author and the publisher cannot assume responsibility for the validity of all materials or for the consequences of their use.

All rights reserved. This book, or any parts thereof, may not be reproduced in any form without written consent from the publisher.

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

© 1991 by CRC Press, Inc.

International Standard Book Number 0-8493-4748-3

Library of Congress Card Number 90-15183
Printed in the United States

P
Chapter 8**EFFECTS OF OCCLUSION*****D. Bucks, R. Guy, and H. Maibach****TABLE OF CONTENTS**

I.	Introduction	86
II.	Percutaneous Absorption of <i>p</i> -Phenylenediamine (PPDA) in Guinea Pigs.....	86
III.	Percutaneous Absorption of Volatile Compounds in Rhesus Monkeys	86
IV.	Percutaneous Absorption of Steroids in Man.....	88
V.	Percutaneous Absorption of Phenols in Man	92
VI.	Discussion	95
	References.....	113

* Sections of this chapter have been adapted from the 2nd edition in this series on Percutaneous Penetration¹¹ and from the doctoral thesis entitled "Prediction of Percutaneous Absorption".¹²

I. INTRODUCTION

Mammalian skin provides a relatively efficient barrier to the ingress of exogenous materials and the egress of endogenous compounds, particularly water. Loss of this vital function results in death from dehydration; compromised function is associated with complications seen in several dermatological disorders. Stratum corneum intercellular lipid domains form a major transport pathway for penetration.^{14-16,22} Perturbation of these lamellar lipids causes skin permeation resistance to fall and has implicated their crucial role in barrier function. Indeed, epidermal sterogenesis appears to be modulated by the skin's barrier requirements.³¹ Despite the fact that the skin is perhaps the most impermeable mammalian membrane, it is semipermeable; as such, the topical application of pharmaceutical agents has been shown to be a viable route of entry into the systemic circulation as well as an obvious choice in the treatment of dermatological ailments. Of the various approaches employed to enhance the percutaneous absorption of drugs, occlusion (defined as the complete impairment of passive transepidermal water loss at the application site) is the simplest and most common method in use.

The increased clinical efficacy of topical drugs caused by covering the site of application was first documented by Garb.²¹ Subsequently, Scholtz³⁶ using fluocinolone acetonide, and Sulzberger and Witten³⁷ using hydrocortisone, reported enhanced corticoid activity with occlusion in the treatment of psoriasis. The enhanced pharmacological effect of topical corticosteroids under occlusion was further demonstrated by the vasoconstriction studies of McKenzie²⁹ and McKenzie and Stoughton.³⁰ Occlusion has also been reported to increase the percutaneous absorption of various other topically applied compounds.^{9,18,26-27} However, as will be shown below, short term occlusion does not necessarily increase the percutaneous absorption of all chemicals.

II. PERCUTANEOUS ABSORPTION OF *p*-PHENYLENEDIAMINE (PPDA) IN GUINEA PIGS

The *in vivo* percutaneous absorption of PPDA from six occlusive patch test systems was investigated by Kim et al.²⁷ The extent of absorption was determined using ¹⁴C radiotracer methodology. The ¹⁴C-PPDA was formulated as 1% PPDA in petrolatum (USP) and applied from each test system at a skin surface dose of 2 mg/cm². Thus, the amount of PPDA was normalized with respect to the surface area of each patch test system (and, hence, to the surface area of treated skin). A sixfold difference in the level of skin absorption ($p < 0.02$) was found (Table 1).

The rate of ¹⁴C excretion following topical application of the radiolabelled PPDA in the various patch test systems is shown in Figure 1. Clearly, the rate and extent of PPDA absorption was dependent upon the occlusive patch test system employed. It should be noted that a nonocclusive control study was not conducted.

III. PERCUTANEOUS ABSORPTION OF VOLATILE COMPOUNDS IN RHESUS MONKEYS

The *in vivo* percutaneous absorption of two fragrances (safrole and cinnamyl anthranilate) and two chemical analogs (cinnamic alcohol and cinnamic acid) were measured under nonoccluded and plastic wrap (Saran Wrap[®]—a chlorinated hydrocarbon polymer) occluded conditions by Bronaugh et al.³ The extent of absorption following single dose administration was determined using ¹⁴C radiotracer methodology. Each compound was applied at a topical dose of 4 µg/cm² from a small volume of acetone. The fragrance materials were well absorbed through monkey skin. Plastic wrap occlusion of the application site resulted in large increases

TABLE 1
Percutaneous Absorption of PPDA from Patch Test Systems^a

Patch test system	mg PPDA in chamber	Mean % dose absorbed (SD)
Hill Top chamber	40	53 (21)
Teflon (control)	16	49 (9)
Small Finn chamber	16	30 (9)
Large Finn chamber	24	23 (7)
AL-Test chamber	20	8 (1)
Small Finn chamber with paper disc insert	16	34 (20)

Note: The rate of ¹⁴C excretion following topical application of the radiolabeled PPDA in the various patch test systems is shown in Figure 1. Clearly, the rate and extent of PPDA absorption was dependent upon the occlusive patch test system employed. It should be noted that a nonocclusive control study was not conducted.

^a 2 mg/mm² PPDA for 48 h on the dorsal mid-lumbar region of the guinea pig.

Data from Kim, H. O., Wester, R. C., McMaster, J. R., Bucks, D. A. W., and Maibach, H. I., *Contact Dermatitis*, 17, 178, 1987.

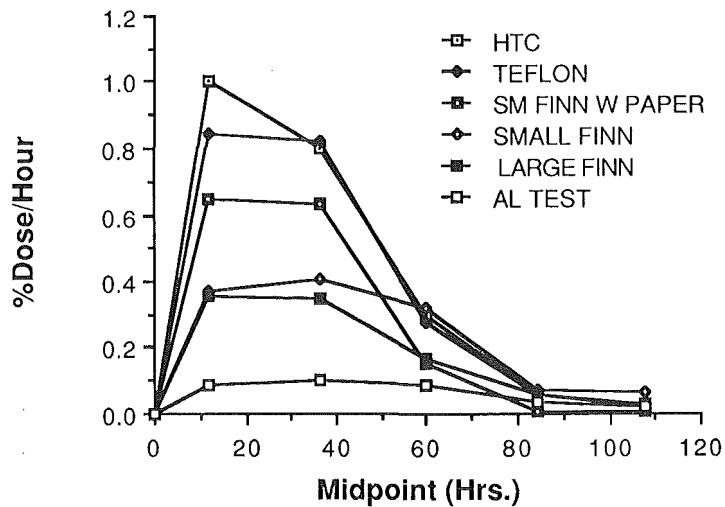


FIGURE 1. *In vivo* percutaneous absorption of PPDA (2 mg/mm²) following a 48 h exposure on the dorsal lumbar region of guinea pigs (Redrawn from Kim, H. O., Wester, R. C., McMaster, J. R., Bucks, D. A. W., and Maibach, H. I., *Contact Dermatitis*, 17, 178, 1987.)

in absorption (see Table 2). The authors also presented *in vitro* data documenting the significant increase in percutaneous absorption of these chemicals under occluded compared to nonoccluded conditions.

Investigation of the effect of occlusion on the percutaneous absorption of six additional volatile compounds (benzyl acetate, benzamide, benzoin, benzophenone, benzyl benzoate, and benzyl alcohol) was conducted using the same *in vivo* methodology. These studies included occlusion of the site of application with a glass cylinder (secured to the skin by

Explore Litigation Insights



Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.