In Vitro Percutaneous Absorption: Principles, Fundamentals, and Applications

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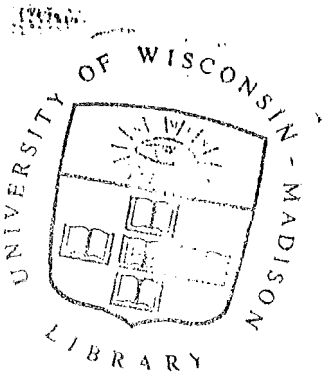

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Chapter 8

EFFECTS OF OCCLUSION*

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TABLE OF CONTENTS

* Sections of this chapter have been adapted from the 2nd edition in this series on Percutaneous Penetration[11] 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 sterologenesis 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, Scholtz[36] using fluocinolone acetonide, and Sulzberger and Witten[37] 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 McKenzie[29] 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 ^{14}C radiotracer methodology. The ^{14}C-PPDA was formulated as 1% PPDA in petrolatum (USP) and applied from each test system at a skin surface dose of 2 mg/cm^2. 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 ^{14}C 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 ^{14}C radiotracer methodology. Each compound was applied at a topical dose of 4 μg/cm^2 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 ^{14}C 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.

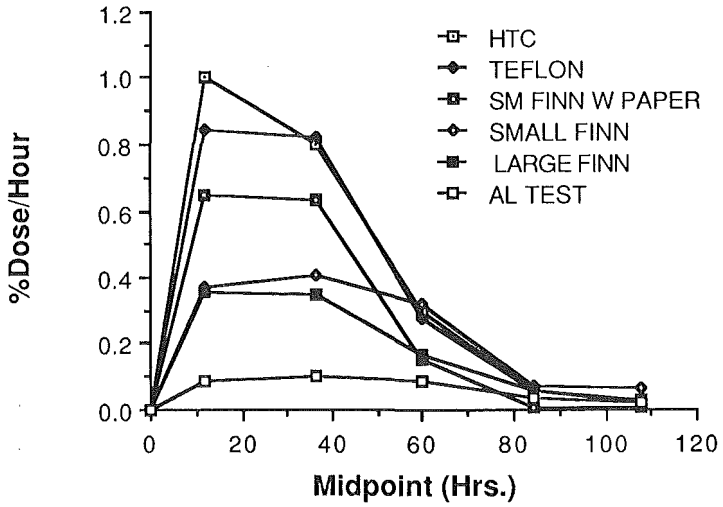

FIGURE 1. *In vivo* percutaneous absorption of PPDA (2 mg/mm²) following a 48 h exposure on the dorsal lumbar region of guinea pigs (Redrawn from Kim, H. O., Wester, R. C., McMaster, J. R., Bucks, D. A. W., and Maibach, H. I., *Contact Dermatitis*, 17, 178, 1987.)

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

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