Effects of Chemical Enhancers on Human Epidermal Membrane: Structure-Enhancement Relationship based on Maximum Enhancement (E_{max})

SARAH A. IBRAHIM, S. KEVIN LI

Division of Pharmaceutical Sciences, College of Pharmacy, University of Cincinnati, Cincinnati, Ohio 45267

Received 3 April 2008; revised 23 May 2008; accepted 24 May 2008

Published online 11 July 2008 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21476

ABSTRACT: Chemical penetration enhancers are widely used in transdermal pharmaceuticals as well as cosmetic products. Selection of suitable enhancers in topical formulations requires an understanding of the mechanism of action of these enhancers. The objective of the present study was to evaluate the enhancement effects of a number of commonly known enhancers and cosmetic ingredients on permeation across human epidermal membrane (HEM). The potencies of these chemical enhancers—maximum enhancement, E_{max}—were compared at their highest thermodynamic activity in equilibrium with HEM (i.e., solubility equilibrium). This was achieved by the treatment of HEM with the enhancer or phosphate buffered saline (PBS) saturated with the enhancer. Passive transport experiments were then conducted with a model permeant corticosterone to determine the effects of these enhancers on the lipoidal pathway of HEM. The results suggest that E_{max} of an enhancer is related to its octanol/water partition coefficient and its solubility in the HEM lipid domain. A relationship between enhancer E_{max} and its solubility in silicone elastomer was also observed, suggesting the use of silicone solubility to predict enhancer potency. Based on the E_{max} results, some common topical ingredients were found to be more potent enhancers than a number of well-known chemical enhancers. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:926–944, 2009

Keywords: chemical enhancers; human epidermal membrane; transdermal permeation; maximum enhancement factor (E_{max})

INTRODUCTION

The effectiveness of a transdermal drug delivery system depends on its ability to deliver the drug at sufficient quantities for a therapeutic effect. In the past three decades, permeation enhancers for transdermal delivery have been extensively studied.[1–4] Over 360 molecules have been shown to enhance the permeation of chemicals across the stratum corneum (SC) and are classified as chemical penetration enhancers. Fatty acids, terpenes, pyrrolidones, and azone are examples of commonly studied transdermal enhancers.[5–10] In general, the mechanisms of chemical enhancers are suggested to be: (a) enhancer perturbation or fluidization of the lipid structure,[11] lipid extraction and solubilization,[12,13] and the modification of the structure of the lipids in SC, (b) protein denaturing effects (such as phenol) on the desmosome thus stripping the squames, which is a dramatic approach not widely accepted,[14] and (c) denaturation of the keratin, keratinocyte swelling, and vacuolation resulting in alteration of the corneocyte in SC.

Earlier transdermal studies of chemical permeation enhancers were mainly focused on enhancer screening. Later studies are focused

Correspondence to: S. Kevin Li (Telephone: 513-558-0977; Fax: 513-558-0978; E-mail: kevin.li@uc.edu)

Journal of Pharmaceutical Sciences, Vol. 98, 926–944 (2009)

on understanding the mechanisms of the enhancers and synergistic effects.[15–17] Attempts have also been made to establish a general relationship between the enhancer structures and enhancer effectiveness.[18–20] It is generally believed that a clear understanding of the mechanism of transdermal permeation enhancement and the establishment of a structure-enhancement relationship would allow the proper selection of enhancers in transdermal formulations. The following are the important findings in our previous studies on the mechanism of transdermal chemical enhancers and their structure-enhancement relationship: (a) the potencies of the enhancers based on their concentrations in aqueous solutions are related to the enhancer octanol–water partition coefficients, (b) the enhancers and their polar head groups are distributed in the SC lipid domain with properties similar to short chain *n*-alkanols, and (c) the intrinsic potencies of the enhancers are essentially the same based on their concentrations in the SC lipid domain independent of the enhancer chemical structures.[21–24] The present study was a continuing effort to evaluate the structure-enhancement relationship based on these findings and hypotheses.[25,26]

The vast majority of chemical enhancers present in transdermal products are highly lipophilic. Due to the lipophilic nature of the enhancers, co-solvents were used in many enhancer studies. Although some co-solvents were shown not to affect the integrity of SC and transport experiments with the co-solvents were used as the control, it is difficult to rule out any potential synergistic effects between the enhancers and co-solvents. The study of enhancers using aqueous media is one approach to avoid possible synergy effects from co-solvents to examine the sole effects of the enhancers, but this method has its limitations. For example, the use of aqueous media to study lipophilic enhancers can be difficult due to rapid depletion of the enhancers in the aqueous media as well as the inability to determine the aqueous free enhancer concentrations. Previous studies have used solubilizing agents as reservoirs to maintain suitable concentration of lipophilic enhancers in aqueous solution.[27,28] However, the use of solubilizing agents can affect the permeability or the integrity of SC. Even if the solubilizing agents do not affect SC permeability, a wide range of control studies is required for the mechanistic interpretation of the data.

In addition to a better mechanistic understanding of the intrinsic effects of the chemical enhancers, the strategy of not using co-solvents and solubilizing agents in an enhancer study can be useful to assess enhancers in a transdermal solution, gel, or aerosol formulation. An aerosol transdermal system has recently been studied.[29,30] The aerosol delivery system is consisted of a fast drying topical solvent with a lipophilic enhancer, so the solvent is not expected to affect skin permeability or provide a solvent-enhancer synergistic effect after solvent evaporation. The use of co-solvents and solubilizing agents is therefore not preferred in the study of the effects of enhancers in this system.

The objectives of the present study were to determine: (a) the effectiveness of the enhancers based on the enhancer maximum enhancement effects, (b) the relationship between the potencies and lipophilicities of these enhancers, and (c) the feasibility of using enhancer solubility in silicone to predict the maximum potencies of the enhancers. The chemical permeation enhancers studied were those commonly used in transdermal products as well as cosmetic products. Permeation enhancers that had been previously studied were also included for comparison because of the unique experimental approach used in the present study. A list of the studied enhancers is provided in Table 1, and their structures are shown in Figure 1. The potencies of the enhancers were evaluated by their maximum intrinsic enhancement effects when the enhancers were presented at their highest thermodynamic activity in equilibrium with HEM. Corticosterone was the model drug because the SC lipid domain was the predominant SC transport rate-determining pathway for corticosterone, and this allowed the direct evaluation of the effects of the chemical enhancers on the SC lipoidal pathway.

EXPERIMENTAL METHODS

Materials

^{3}H-corticosterone (CS) at purity >97% was purchased from Perkin Elmer Life and Analytical Sciences (Boston, MA) and American Radiolabeled Chemicals, Inc. (St. Louis, MO). Isopropyl myristate and *n*-hexanol were obtained from Alfa Aeser (Ward Hill, MA) at purity >98%. Oleyl alcohol was obtained from Alfa Aeser at purity >85%. *n*-Octanol, 2-phenoxyethanol, butylated hydroxyanisole, salicyaldehyde, 1-undecanol, and sodium azide (NaN_3) were obtained at purities