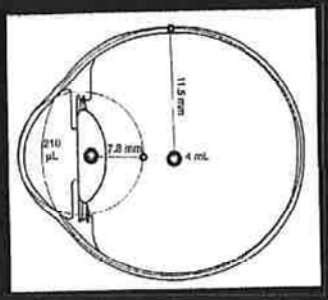
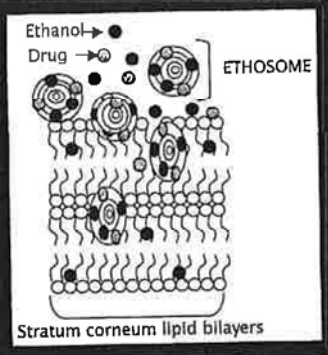
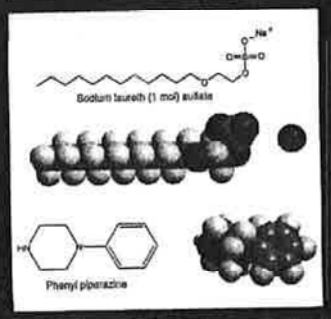
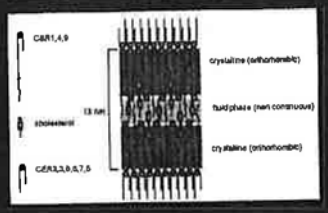
Enhancement *in* Drug Delivery









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12 Chemical Permeation Enhancement

Adrian C. Williams and Brian W. Barry

CONTENTS

12.1 INTRODUCTION

Among the myriad strategies employed to increase both the amount of a therapeutic agent traversing the skin and the range of drugs that can be effectively delivered through this route, lies in the application of chemical penetration enhancers. These agents interact with stratum corneum constituents to promote drug flux. Such materials have been used empirically in topical and transdermal preparations for as long as pastes, poultices, creams, and ointments have been applied to skin, though it is only over the last four decades that enhancers have been employed deliberately for this specific purpose. To date, nearly 400 chemicals have been evaluated as penetration enhancers (accelerants, absorption promoters), yet their inclusion into topical or transdermal formulations is limited because the underlying mechanisms of action of these agents are seldom clearly defined and regulatory approval is costly and difficult. Here, we review some applications of the more widely investigated chemical penetration enhancers and consider some of the complex mechanisms by which they may exert their activities.

mixtures of enhancers that increased the skin permeability to macromolecules, such as heparin, luteinizing hormone-releasing hormone, and an oligonucleotides, by up to 100-fold. The two most successful SCOPE formulations were a mixture of sodium laureth sulfate with phenyl piperazine (Figure 12.7a) and a combination of *N*-lauroyl sarcosine with sorbitan monolaurate (Figure 12.7b).

Future work may elucidate why the areas of potency hot spots were so restricted, and the fundamental molecular mechanisms producing the enhancement. The molecular structures of the most successful SCOPE mixtures, as illustrated in Figure 12.7, suggest that surface-active phenomena may play a crucial role.

Instead of using a screening approach, with its heavy workload, investigators have tried other techniques. Many studies demonstrated that a rule-based approach to enhancement was fraught with difficulties; enhancer combinations in different vehicles for specific permeants traversing a particular membrane thus tend to be evaluated on a case-by-case basis [72,73]. However, attempts have been made at a more rational approach to enhancer selection, applying quantitative (and qualitative) structure–activity relationships to penetration enhancers [74–77]. Naturally, such models depend upon the quality of data used to obtain the relationship. Hence inclusion of information derived from, for example, different animal models or dosing regimens must be carefully assessed as the generated relationship may only be applicable to the specific conditions used in obtaining the input data.

12.4 GENERAL COMMENTS ON PENETRATION ENHANCERS

The list of materials that have been used as penetration enhancers as discussed above is not exhaustive but is intended to illustrate the range of agents that have been employed for facilitating transdermal drug delivery. Several common themes emerge from these considerations:

1. It is difficult to select rationally a penetration enhancer for a given permeant. Accelerant potencies appear to be drug specific, or at best may be predictive for a series of permeants with similar physicochemical properties (such as similar partition coefficients, molecular weights, and solubilities). Some broad trends are apparent, such as the use of hydrocarbon monoterpenes for lipophilic permeants, but the level of enhancement expected for these agents is unpredictable.
2. Penetration enhancements through animal skins, and rodent tissues in particular, are generally considerably greater than those obtained with human skin, correlating with the increased barrier resistance of human stratum corneum. Hairless mouse skin is particularly fragile and its use may grossly mislead the investigator. Most experiments are performed *in vitro*, although there are exceptions, for example, the use of confocal Raman spectroscopy to monitor the penetration of DMSO through volunteer skin [78].
3. Accelerants tend to work well with cosolvents such as PG or ethanol. Synergistic effects arise enhancers such as azone, oleic acid (and other fatty acids), and terpenes dissolved in, for example, PG.
4. Many enhancers have a complex concentration-dependent effect. This is shown clearly by azone, which is effective in promoting the transdermal flux of many drugs when used at 1% in PG but which is far less potent when applied at higher concentrations or neat.
5. Potential mechanisms of action of enhancers are varied, and can range from direct effects on the skin to modification of the formulation. Thus, directly acting on the skin, enhancers can do the following (see Figure 12.1):
   (i) Modify the intercellular lipid domains to reduce the barrier resistance of the bilayer lipids. Disruption to the lipid bilayers could be homogeneous where the enhancer

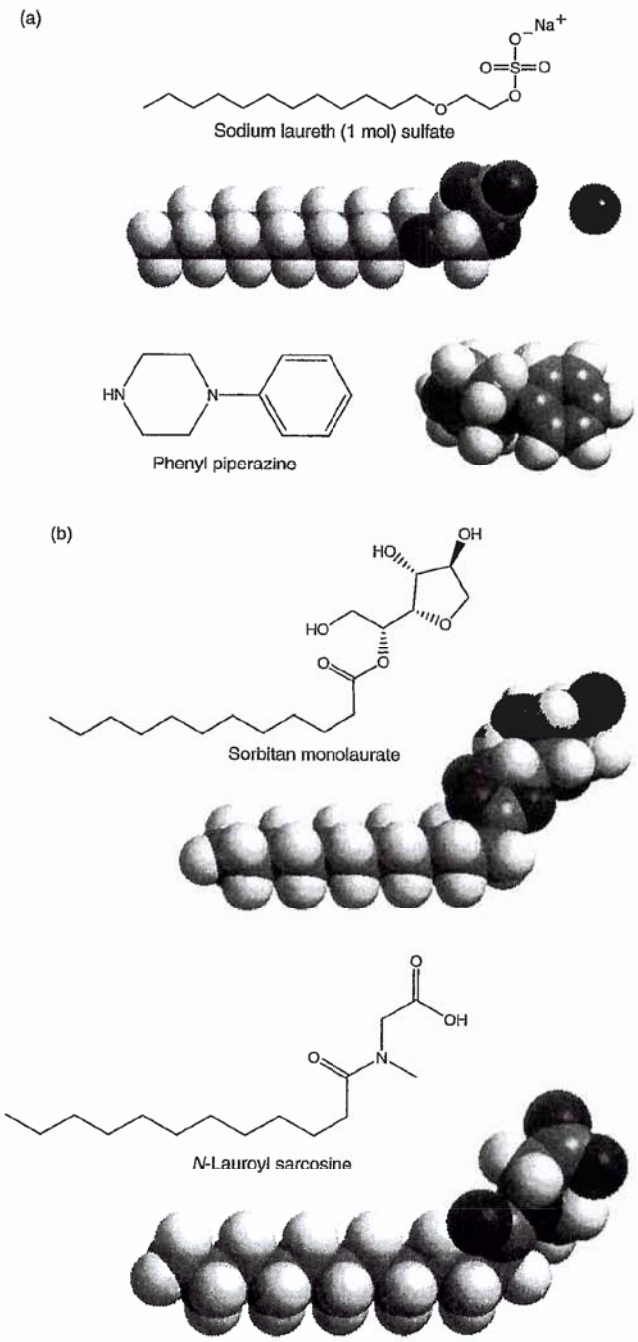

FIGURE 12.7 The two most potent SCOPE formulations. (a) A mixture of sodium laureth sulfate with phenyl piperazine and (b) a combination of sodium monolaurate with *N*-lauroyl sarcosine. (From Karande, P., Jain, A. and Mitragotri, S. *Nat Biotechnol* 22:192, 2004.)

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