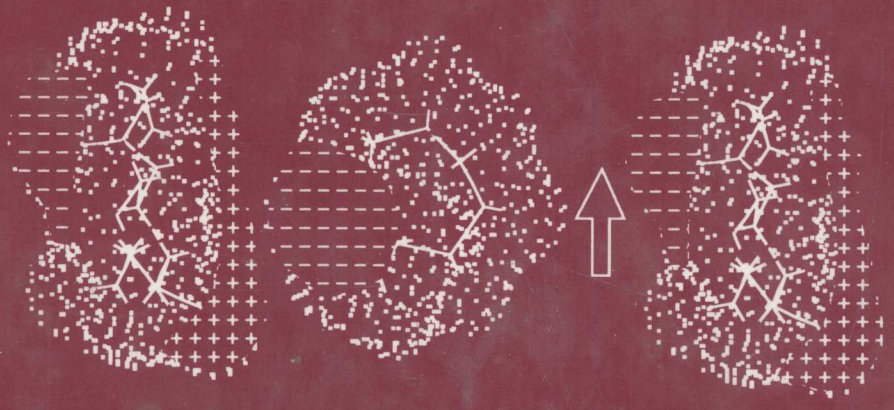
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 59

Pharmaceutical Skin Penetration Enhancement



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Pharmaceutical Skin Penetration Enhancement

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Preface

Over the past decade, the interest in skin penetration has blossomed, primarily as a result of the developments in transdermal drug delivery systems and their perceived advantages over conventional drug therapy. To optimize the formulation of such systems, and also those used in topical therapy, it has been necessary to gain a better understanding of the mechanisms of skin penetration. This has been facilitated by the advent of more sophisticated physicochemical instrumentation such as Fourier transform infrared spectroscopy, nuclear magnetic resonance spectroscopy, electron spin resonance, and other spectroscopic techniques that now have the precision and sensitivity to probe the complex nature of the skin. The mechanistic evaluation at a molecular level has resulted in a better understanding of the route of drug penetration through the stratum corneum and the physicochemical factors that control the rate of transport through this complex membrane.

Penetration enhancers have been examined for several years and, again, their significance has become greater with the developments of transdermal delivery. Two decades ago the most significant penetration enhancers were probably the dipolar aprotic materials, such as dimethyl sulfoxide and dimethyl acetamide. The former is a very potent enhancer of many drugs, and our understanding of its precise mechanism of action has still not been fully clarified. The spectroscopic techniques mentioned have been used extensively in trying to establish precise mechanisms of action for the many enhancers that have now been identified.

Because of their widely differing chemical structures, it is apparent that they act by more than one mechanism and that their precise enhancer activity will depend on the physicochemical properties of the penetrant. Owing to the application of fundamental physicochemical concepts to the skin transport process, it is becoming possible to identify the features that an enhancer should possess to have optimal activity.

In this book, contributions have been sought to represent the different types of enhancer that have been identified. Not only has the use of chemical enhancers been addressed, chapters have also been contributed on the use of physical enhancement using the processes of iontophoresis and phonophoresis. Authors have been chosen who are at the forefront of research in their individual areas and who, where possible, put a mechanistic interpretation on the ways in which enhancers act. We feel that it is only with an understanding, at a molecular level, that significant advances can be made in the future development of enhancer strategies for transdermal and topical therapy. The book has been written both to answer specific questions and to highlight the ways in which our future research can be directed in a fruitful and challenging fashion. In the future, our ability to probe the skin will become more refined, and it may be possible to use molecular graphics to design drugs that act as their own enhancers. This book lays the groundwork for this promising future.

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Contents

1

Water

The Most Natural Penetration Enhancer

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The state of hydration of the stratum corneum (SC) is one of the most important factors in determining the rate of percutaneous absorption of a given solute. The level of hydration is a function of the water concentration gradient between the dermis and the surface of the skin as well as on the ability of the stratum corneum to "bind" the water. Many of the environmental, physiological, and pharmacological factors modifying skin hydration can be related to their effects on the water concentration gradient across the stratum corneum

In a practical sense, hydration of the skin is an important determinant of the skin texture ("softness") and appearance. Many dermatological disorders affect the extent to which stratum corneum binds the water for hydration.

I. WATER CONCENTRATION GRADIENT IN THE STRATUM CORNEUM

The SC represents a distinct phase between the environment and the epidermis. Transfer of water at the SC–environment and SC–lower epidermis interface (i.e., *absorption*) occurs much faster than diffusion through the SC (1,2). The overall water gradient in the SC, therefore, is determined by the diffusivity of water in the SC and the thickness of the SC.

The SC water content, at normal relative humidities, is between 15 and 20% of dry weight. Soaking, occlusion and high humidities may increase the water

content further—up to 300–400% of the dry weight after extensive soaking. An increase in water content results in an increased elasticity and permeability of SC, whereas reducing the water content will lead to an opposite effect. Very dry SC loses its elasticity and fissures under stress, as observed in many dry skin conditions.

The transepidermal water loss (TEWL) reflects the continuous diffusion of water from within the body through the SC to the ambient environment. With an increase in the environmental humidity, the concentration difference of water between the inner and outer surface of the SC is diminished and the TEWL is reduced. The normal TEWL is about 0.5 $\mu L \cdot cm^{-2} \cdot hr^{-1}$. The SC water content decreases when the percentage relative humidity (RH) is decreased, and the skin flexibility is reduced at RH values below 60% (3). The amount of water per gram of dry tissue in human SC is 0.2 g and 0.7 g for relative humidities of 40 and 70%, respectively (4). The skin will become brittle when the water content is less than 10% (3). Increased water loss also occurs as the temperature is increased or when air flows over the skin. These observations, deduced using isolated skin specimens (3), have also been confirmed in clinical studies (5). Singer and Vinson (6) have suggested that the water content of neonatal rat skin varied with RH in a logarithmic manner and was independent of the absolute humidity (Fig. 1).

In the in vivo situation, the SC is sandwiched between the aqueous lower layers of the skin and the ambient environment, which may be very dry. As a consequence, the lower layers adjacent to the granular layer are highly hydrated, whereas the surface layers contain less water. The cell layer of SC in equilibrium with the viable epidermis is expected to contain between 5 and 6 g water per gram of dry tissue (4). Given a water content of 0.2 g/g dry SC for 40% RH, Scheuplein and Blank suggest that the average SC water content in vivo from a 40% RH is 0.92 g/g dry tissue (4). An increase in the ambient or atmospheric water content results in a reduction in the water gradient across the SC so that if a completely occlusive aqueous vehicle is applied to the SC surface, it should eventually yield a uniform water concentration throughout the SC. A similar SC water–distance profile would be anticipated for a side-by-side diffusion cell. However, in both cases, water uptake and swelling continues for about 3 days (4).

II. STATE OF WATER IN THE STRATUM CORNEUM

An increase in hydration of the skin is associated with a swelling of the stratum corneum and a softening of its texture. Consistent with its low diffusion coefficient in SC, water does not ooze from the surface of freshly excised skin. Most studies have used direct-weighing techniques to define the "water holding" capacity of the SC (6,9). Figure 2a shows the topography of the skin before and Figure 2b shows it after hydration following the application of a plastic occlusive