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Computational Methods for Prodrug or Drug Analogue Selection Optimized for Percutaneous Delivery

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I. INTRODUCTION

The introduction of transdermal patch systems capable of delivering therapeutic systemic levels of clonidine, nitroglycerin, estradiol, and scopolamine (1,2) has caused the realization that the skin is an alternative route for drug administration. For the topical formulator, an important result of the work conducted on patch systems is that models are available that can predict the rate at which a drug can cross the stratum corneum barrier. Although topical formulations will seldom try to maintain systemic drug levels, localized delivery of a drug will require that the stratum corneum barrier be crossed. Thus, it is important to know the flux value of the drug across the stratum corneum. By having this information early during development of the formulation, timely discussions of drug concentration within the formulation can be completed. The need for addition of absorption enhancers to the formulation can also be determined.

Recently four empirical models were evaluated to determine their ability to predict percutaneous absorption of drugs (3). Two of the predictive models evaluated were developed by Berner and Cooper (4), the third was taken from a publication by Michaels et al. (5), and the fourth was proposed by Albery and Hadgraft (6,7). In this previous study, ten drugs, having a wide range of physical properties, were evaluated and their resulting predicted transdermal flux values compared with experimental values. These permeation equations are useful for predicting the flux of a drug through the skin barrier when values for the water solubility, partition coefficient, and molecular weight of the drug are known. However,