1. INTRODUCTION

Percutaneous absorption has been studied in great detail over the two past decades, owing to the synthesis and development of potent topical drugs and the recent interest in transdermal drug delivery systems. Research in this area has intensified because of concern about systemic exposure to potentially toxic agents. Moreover, it is now well accepted that penetration of substances is sometimes desirable because of both local and systemic effects. However, from a practical viewpoint a major problem in the study of skin permeability is the interpretation of results. As this kind of research has interested scientists from widely differing disciplines, workers have chosen or adapted the methodology used in order to elucidate their specific problem. Thus, it remains difficult to draw valid conclusions from the literature concerning the absorption level of a given compound. This is essentially due to the diversity of techniques used, differing in the choice of animal species, anatomical location, duration of application, dose applied, and vehicle used. Moreover, the ideal way to assess the penetration potential of a drug in humans is to do the actual study in humans. However, many compounds are potentially too toxic to be tested in vivo in humans, and extrapolation from animal studies to humans is still problematic.

From a theoretical viewpoint, much work has been done to elucidate skin structure, physiology, barrier properties, and mechanisms by which substances
enter and cross the skin. The different theories of skin absorption mechanisms will not be considered here. It is well established that the main barrier is constituted by the stratum corneum (S.C.), which also acts as a "reservoir" for topically applied substances. Moreover, it is likely that, at an early step of the absorption process, the interaction between the physicochemical properties of the drug, the vehicle, and the horny layer (i.e., partitioning of the drug between the vehicle and the horny layer) plays an important role.

In the first part of this chapter, we aim to establish the relationship existing between the reservoir effect of the horny layer and percutaneous absorption of molecules. We hypothesize that the amount of chemical present in the stratum corneum at the end of application may represent the stratum corneum–vehicle partitioning and could also reflect the rate of penetration of the chemical. In the second part, we demonstrate that this hypothesis is independent of the main factors likely to modify the absorption level of a compound, i.e., contact time, dose applied, vehicle used, anatomical site involved, and animal species chosen.

2. IN VIVO RELATIONSHIP BETWEEN STRATUM CORNEUM CONCENTRATION AND PERCUTANEOUS ABSORPTION

We chose to test, on the hairless rat, 10 radiolabeled substances having very different physicochemical properties and belonging to different chemical classes: dexamethasone, hydrocortisone, dehydroepiandrosterone, testosterone, acetylsalicylic acid, sodium salicylate, caffeine, benzoic acid, mannitol, and thiourea. Two hundred nanomoles of each substance dissolved in an ethanol–water mixture were applied onto 1 cm² of dorsal skin. After 30 minutes of application, the excess was rapidly removed by washing (ethanol–water), rinsing (water), and drying the treated area.

On a first group of animals, the total amount of substance penetrating within 4 days was determined by adding the amounts found in the excreta (urine + feces), in the epidermis and dermis of the application area, and in the whole animal body (global method) (Figure 1).

At the end of application (30 minutes) and after washing, the S.C. of the treated area of the animals from a second group was removed by 6 strippings using 3M adhesive tape. In our experimental conditions, the capacity of the S.C. reservoir for each compound has been defined as the sum of the amounts found in the first 6 strippings (stripping method) (Figure 1).

The percutaneous absorption results show (Figure 2) that after 96 hours there are large differences in the amounts of substances that have penetrated through the skin. Thus, one can observe that the most penetrating molecule, benzoic acid, penetrates 50 times more than dexamethasone. The formation of a significant substance reservoir within the horny layer may be due to the existence