

These general statements apply to skin in the normal state. Skin that is abraded or cut permits drugs to gain direct access to the subcutaneous tissues and the capillary network, defeating the function of the TDDS.

PERCUTANEOUS ABSORPTION ENHANCERS

There is great interest among pharmaceutical scientists to develop chemical permeation enhancers and physical methods that can increase percutaneous absorption of therapeutic agents.

Chemical Enhancers

By definition, a chemical skin penetration enhancer *increases skin permeability by reversibly damaging or altering the physicochemical nature of the stratum corneum to reduce its diffusional resistance* (12). Among the alterations are increased hydration of the stratum corneum, a change in the structure of the lipids and lipoproteins in the intercellular channels through solvent action or denaturation, or both (4,13–17).

Some drugs have an inherent capacity to permeate the skin without chemical enhancers. However, when this is not the case, chemical permeation enhancers may render an otherwise impenetrable substance useful in transdermal drug delivery (17). More than 275 chemical compounds have been cited in the literature as skin penetration enhancers; they include acetone, azone, dimethylacetamide, dimethylformamide, dimethyl sulfoxide, ethanol, oleic acid, polyethylene glycol, propylene glycol, and sodium lauryl sulfate (13–15). The selection of a permeation enhancer should be based not only on its efficacy in enhancing skin permeation but also on its dermal toxicity (low) and its physicochemical and biologic compatibility with the system's other components (16).

Iontophoresis and Sonophoresis

In addition to chemical means, some physical methods are being used to enhance transdermal drug delivery and penetration, namely, iontophoresis and sonophoresis (6,15,18–23).

Iontophoresis is delivery of a charged chemical compound across the skin membrane using an electrical field. A number of drugs have been the subject of iontophoretic studies; they include lidocaine (18); dexamethasone; amino acids, peptides, and insulin (19,20); verapamil (6); and propranolol (21). There is particular interest to develop alternative routes for delivery of biologically active peptides. At present, these agents are delivered by injection because of their rapid metabolism and poor absorption after oral delivery. They are also poorly absorbed by the transdermal route because of their large molecular size and ionic character and the general impenetrability of the skin (20). However, iontophoresis-enhanced transdermal delivery has shown some promise as a means of peptide and protein administration.

Sonophoresis, or high-frequency ultrasound, is also being studied as a means to enhance transdermal drug delivery (22,23). Among the agents examined are hydrocortisone, lidocaine, and salicylic acid in such formulations as gels, creams, and lotions. It is thought that high-frequency ultrasound can influence the integrity of the stratum corneum and thus affect its penetrability.

PERCUTANEOUS ABSORPTION MODELS

Skin permeability and percutaneous absorption have been the subject of numerous studies to define the underlying principles and to optimize transdermal drug delivery. Although many experimental methods and models have been used, they tend to fall into one of two categories, *in vivo* or *in vitro*.

In Vivo Studies

In vivo skin penetration studies may be undertaken for one or more of the following purposes (24):

1. To verify and quantify the cutaneous bioavailability of a topically applied drug
2. To verify and quantify the systemic bioavailability of a transdermal drug
3. To establish bioequivalence of different topical formulations of the same drug substance