The barrier function of the skin in relation to percutaneous absorption of drugs

J.W. Wiechers

Introduction
The skin is the outermost and one of the most easily accessible organs of man, yet one of the most neglected organs by pharmacists for a long time. The pharmaceutical interest remained limited to topical treatment of dermatological diseases, such as psoriasis, acne and dermatitis. It was only after the recognition of the skin as an alternative port of entry for systemically acting drugs that much more attention was paid to this organ.

Topical application of drugs for systemic therapy may have several advantages over the conventional oral route. It circumvents variables that may influence the gastro-intestinal absorption, such as the drastic changes in pH along the gastrointestinal tract, food intake, intestinal motility etc. Additionally, it may eliminate systemic first-pass metabolism as it circumvents the liver, thereby increasing the bioavailability of drugs susceptible to this bioconversion. Delivering drugs by the transdermal route may provide controlled, constant administration of the drug, allowing continuous input of drugs with short biological half-lives. This would, in turn, improve patient compliance, since frequent intake of the drug is no longer necessary. The transdermal route can also eliminate pulsed entry into the systemic circulation, which can often cause undesirable side effects [1 2].

Transdermal therapy, however, also has its limitations. Firstly, and foremost, the skin acts as a barrier in two directions, controlling the loss of water, electrolytes, and other body constituents, while preventing the entry of harmful or unwanted molecules from the external environment [1]. Secondly, there may be pharmacodynamic, physiological and/or physico-chemical limitations. Compounds may act as irritants (sodium lauryl sulphate), cause allergic sensitization (some antibiotics), hyperpigmentation (bleomycin), or be keratolytic (salicylates) [2 3]. These pharmacodynamic effects are dependent on the extent of the percutaneous absorption of the substance in question, which, in turn, depends on the physiological characteristics of the skin and the physico-chemical properties of the penetrant. In general, the maximally obtainable flux is estimated to be a few milligrams per day.

Factors that influence the percutaneous absorption of chemicals through the skin are:
- the structure of the skin;
- the physico-chemical characteristics of the penetrant;
- the physico-chemical characteristics of the vehicle in which the penetrant is dosed;
- the dosing conditions.

These will be discussed in more detail in the following sections.

It will become apparent that transdermal drug delivery is a very complex issue, as there are many variables involved that are often strongly interrelated. Nevertheless, this complexity can be unravelled to a certain extent by a systematic approach to the most important parameters that influence percutaneous absorption. For a good understanding of the issue, some common terms will be defined here. Percutaneous absorption is the uptake of a compound into the systemic circulation after dermal application, and describes the movement through the various layers of the skin with

Keywords
Absorption, skin
Administration, topical
Permeability, enhancement

Dr. J.W. Wiechers: Groningen Centre for Drug Research, Bio-analysis and Toxicology Group, University of Groningen, Ant. Deusinglaan 2, 9713 AW Groningen, the Netherlands. Present address: Unilever Research, Colworth Laboratory, Sharnbrook, Bedford MK44 1LQ, England.


Abstract
There is currently a high level of interest in using the skin as a route for delivering drugs. The skin, however, provides an efficient barrier against percutaneous absorption of drugs. This barrier function can be ascribed to the macroscopical structure of the stratum corneum, which consists of alternating lipoidal and hydrophylic regions. For this reason, physico-chemical characteristics of the drug, such as partition coefficient and molecular weight, play an important role in determining the facility of percutaneous absorption. Another factor to consider in transdermal drug delivery, is the vehicle in which the drug is formulated as it acts on the release of drug from the formulation. Moreover, vehicles may also interact with human stratum corneum, thereby affecting its barrier function. Surfactants and penetration enhancers are well-known examples of the latter. Subsequently, dosing conditions, such as humidity, temperature and occlusion, also have their impact on the actual input (rate) of drug through human skin. Finally, all bits of information are combined to form a reasonably faithful picture of percutaneous absorption.

Received June 1989, revised August 1989, accepted September 1989.
respect to both rate and extent. The percutaneous absorption process can be divided into three steps [3]:
- penetration, which is the entry of a substance into a particular layer or organ;
- permeation, which is the penetration through one layer into another, which is both functionally and structurally different from the first layer;
- absorption, which is the uptake of a substance into the vascular system (lymph and/or blood vessel), which acts as the central compartment.

**Structure of the skin**

**Anatomy and physiology of human skin**

Before reaching the systemic circulation, a penetrating chemical has to cross several potential barriers. These include the epidermis (consisting of the stratum corneum or horny layer and the viable layers of the epidermis) and the dermis.

The stratum corneum. The outermost layer of the skin, the horny layer or stratum corneum, has been identified as the principal barrier for penetration of most drugs [4]. The stratum corneum is about 10 μm thick in the non-hydrated state and contains 10 to 25 layers, parallel to the skin surface, consisting of dead, keratinized cells, called corneocytes [1]. It is flexible, yet impermeable. The horny pads of the palms of the hand and foot-soles are adapted for weight-bearing and friction. Here, the stratum corneum is much thicker, on average 400-600 μm, with vertically stacked cells [1].

There are various potential pathways for permeation through the stratum corneum. The transappendageal route comprises transport via the sweat glands and along the hair follicles with their associated sebaceous glands (Fig. 1). These routes circumvent penetration into the stratum corneum itself and are therefore known as 'shunt routes'. The transepidermal route across the continuous stratum corneum between the appendages comprises transport via the intercellular spaces and by the intracellular or transcellular route through the cells themselves [5] as depicted in Figure 2.

The appendageal route along hair follicles, sebaceous glands and sweat glands is considered to be of minor importance because of their relatively small area (less than 0.1% of the total surface). Moreover, the presence or absence of hair follicles and glands does not significantly influence the extent of percutaneous penetration [6], and is only noticeable in the early stages of percutaneous absorption [7]. However, this route may be of some importance for ionic molecules or large polar compounds [8].

The intercellular spaces are filled with two alternating layers. One of these layers contains lipids, such as ceramides, sterols (predominantly cholesterol), sterol esters (e.g. cholesteryl sulphate) and free fatty acids, which are organized in multilaminated sheets [9]. Bilayers as such are not sufficient to account for the water impermeability, as typical biological bilayers consisting of phospholipids are known to permit free passage of water molecules. However, the bilayers in the intercellular spaces in the stratum corneum consist of straight, closely packed, and almost entirely saturated hydrocarbon chains, without structural perturbation among the hydrophobic chains. This highly ordered, rigid structure results in a unique impermeability for many compounds including water [10]. The hydrocarbon chains alternate with watery channels as shown in Figure 2, which comprise the polar route through the bilayer.

The intracellular spaces consist of cornified cells, called corneocytes, which are bounded by an envelope having a more lipidoid exterior, which anchors them to the intercellular lipid lamellae, and a more hydrophylic interior [11]. The corneocytes, constituting by far the larger volume of the stratum corneum, are covered with keratin filaments (i.e. cytoplasmic protein, consisting of disulfide cross-linked linear poly-peptides). There are some lipids and carbohydrates in the cell, most of them being present as lipoproteins and glycoproteins, respectively [12]. The proteins can be divided in a water-soluble and a water-insoluble cell membrane fraction. All components of the intracellular spaces, except for the water-soluble proteins, contribute to the barrier function of the stratum corneum [13].

Nowadays, the stratum corneum is seen as a wall-like structure with protein bricks and lipid mortar [14]. The lipid matrix plays the more important role in the functioning of the barrier. Extraction of the intercellular lipids decreases the barrier function dramatically, while keratolytic agents provoke only a minor response [13]. The protein phase is discontinuous while the lipid phase is continuous, yet very convoluted. This results in a long and tortuous pathway for any molecule moving through the stratum cor-