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Percutaneous absorption of drugs

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Percutaneous absorption is the passage of drugs through the cutaneous structures and the extracellular medium from the outside to the bloodstream. This phenomenon consists of two steps: (1) A penetration phase, i.e. the passage of molecules through the superficial skin structures, the *stratum corneum* and the epidermis, to the extracellular medium. (2) A resorption phase during which a relatively rapid diffusion occurs from extracellular fluid to the blood by way of cutaneous microcirculation[1,2].

If the resorption phase is analogous to that observed during any absorption process, the skin penetration phase is very special. In fact, skin exhibits a superficial 'rate-limiting barrier', which only enables drug penetration at a very slow rate. Through increased knowledge of the properties of this barrier, it is now possible to understand and explain the various aspects of percutaneous absorption of drugs.

The rate-limiting barrier

The principal 'barrier' function of the skin resides almost entirely in the *stratum corneum* (thin coherent membrane of keratinized dead cells) which prevents the penetration of chemical substances. This has been proved by various experiments: the skin deprived of the *stratum corneum* is very permeable (Table I); the isolated *stratum corneum* is almost as impermeable as the entire skin. Finally, dead skin used in *in vitro* experiments exhibits almost the same permeability as living skin, thus showing that living cells of epidermis do not contribute greatly to skin impermeability[8].

The structure of the *stratum corneum* explains this barrier effect (Fig. 1). The *stratum corneum* consists of 10–20 layers formed and continuously replaced, of

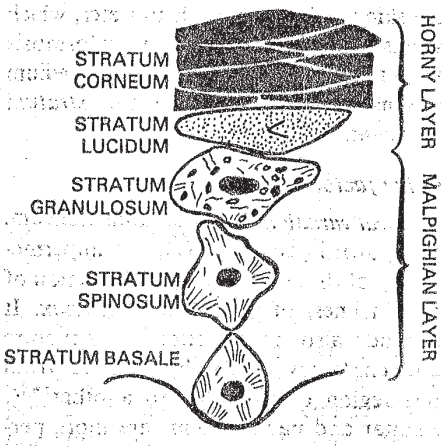

Fig. 1. Schematic representation of the evolution of epidermal cells.

flattened keratinized cells from the underlying living epidermis[5]. Adhesion between cells occurs at the level of the altered desmosomes which are tight junctional zones between living cells of epidermis. Each cell (Fig. 2) has a thick membrane, which is the most efficient component of the protective system. It is resistant to keratolytic agents, most of the proteases, diluted strong acids and bases. The inner part of the cells contains α-keratin filaments, 6–8 nm in diameter, representing 50% of the cellular content. The fibrous protein is embedded in a proteic amorphous matrix rich in disulphide bonds. This structure exhibits a high resistance to chemical agents but is destroyed by keratolytic reducing agents, strong acids and bases. The cell also contains structural lipids and water soluble substances which allow hydration of the *stratum corneum*. Finally, the intercellular spaces are filled by lipids of lamellar structure released during the keratinization process by granules called 'membrane coating granules'. The diffusion of aqueous solutes is controlled by these lipid layers.

Hence the *stratum corneum* is a very densely packed structure which effectively prevents the penetration of chemical substances. It can almost be described as a mosaic of elements with hydrophilic properties which are able slowly to trap water. These elements are embedded in the lipids which fill the intercellular space and form a continuous structure with a very low permeability to water-soluble substances.

TABLE I. Importance of *stratum corneum* on the permeability of skin as shown by the ratio K_p across skin without *stratum corneum*/K_p across whole skin.

Substance	Species	Reference	Ratio
Water	Human	3–7	20 to 100
Ethanol	Mouse	Personal results	20
Estradiol	Human	3	15
Amphetamine	Human	3	6600
Trichlorocarbanilide	Human	Personal results	2 to 5

Absorption theory

From the literature, it is clear that absorption of drugs occurs by passive diffusion[7]. The living cells of the epidermis are relatively more permeable than the *stratum corneum* and do not appear to intervene except in certain cases. The horny layer remains the rate-limiting factor of absorption. For solutions of low molecular weight drugs, at least slightly water soluble, an expanded law derived from Fick's law at steady-state transport can be applied:

$$J = K_p . \Delta C = \frac{D \times k_1}{e} . \Delta C \qquad (1)$$

where:

J = the flux of the penetrating drug (quantity of drug absorbed per unit of area and unit of time),
K_p = permeability constant,
ΔC = difference between concentration above (C_1) and below (C_2) the membrane (C_2 is generally negligible compared to C_1),
D = diffusion constant of the drug in the *stratum corneum*,
k_1 = *stratum corneum*/vehicle partition coefficient of the drug,
e = thickness of the *stratum corneum*.

Equation (1) summarizes the elementary physics of the penetration process through the skin. Even though it is an oversimplification, it includes the main important factors explaining percutaneous absorption of drugs.

The absorption intensity is thus proportional to the concentration of the dissolved drug in the vehicle and to the application area. Using the same quantity of drug, the systemic effects will be greater in proportion with the area of skin covered.

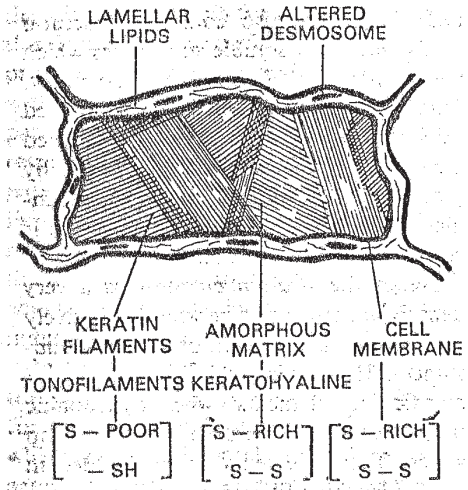

Fig. 2. Schematic illustration of the structure and chemical components of horny cell and intercellular substance in the stratum corneum.

Importance of the diffusion coefficient

The diffusion constant represents the rate of migration of a drug through the horny layer. It is inversely proportional to both size of the molecules and viscosity of the medium. The *stratum corneum* exhibits a very high apparent viscosity so the diffusion constant of the molecules is very low, being between 10^{-9} cm^2 s^{-1} for alcohols and 10^{-12} to 10^{-13} cm^2 s^{-1} for steroids[7]. These values are much higher in the living layers of the skin: 10^{-6} cm^2 s^{-1}. This explains why the *stratum corneum* is the rate-limiting factor of percutaneous absorption.

As the *stratum corneum* has non-negligible thickness (20–40 μm), there is a period of transient diffusion (lag time) after applying a drug to the skin, during which the rate of transfer through the skin rises to reach a steady rate (Fig. 3). The steady state is maintained thereafter indefinitely, provided the system is constant. On the skin, the lag time is often prolonged and reaches several hours[2,8].

Partition coefficient: stratum corneum/*vehicle*

The partition coefficient k_1 of the drug between *stratum corneum* in Fick's law, shows the importance of the solubility characteristics for a substance to penetrate the skin.

Because of the presence of intercellular lipids, the *stratum corneum* exhibits the characteristics of a lipophilic structure. Many experiments have shown a direct relation between lipophilic solvent (representing *stratum corneum*) and water partition coefficient of an aqueous solute and its permeability constant[7–9]. Better results are often obtained by measuring this partition between sheets or powder of isolated *stratum corneum* and water, or another vehicle containing the drug in solution[7,12].

When k_1 is high, the drug accumulates in the *stratum corneum* and a significant concentration of drug appears at the point of contact with the living cells. At this level, penetration is rapid by migration in the intercellular spaces (which are large in the living epidermis) assuming that the substance is at least slightly soluble in water. However, with purely lipophilic substances, the penetration does not go further than the *stratum corneum*. For instance, triglycerides and perhydrosqualene are very poorly absorbed by the skin[12]. For water-soluble drugs, absorption is very low, the limiting barrier being located in the *stratum corneum*. However, the skin is fairly permeable to water, which seems capable of diffusion by osmosis from the outside or from the inner medium (insensible water loss) to the *stratum corneum*.

Other factors

Local variations of the stratum corneum. As shown in equation (1), the impermeability of the skin is an inverse function of the thickness of the *stratum corneum*. It depends also on variations in structure and chemistry of the horny-layer from one region of the body to another[7,8,12]. Plantar and palmar callus are more permeable than the *stratum corneum* of other parts of the body. Permeability, as will be seen below, increases with number of hair follicles present in the skin. These factors explain variations in the permeability of the skin of different parts of the body, which can be classified by order of increasing diffusional resistance, as follows, palm skin, scrotum, posterior part of ear, axillary regions, scalp, arms, legs and chest. There are large individual variations in skin permeability in which age and racial factors seem to play an important role. Pathological skin (eczema, psoriasis)

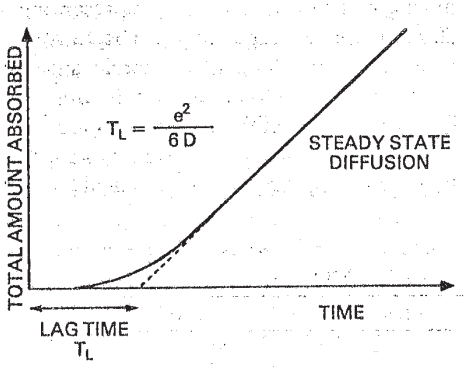

Fig. 3. Time course of penetration for drug diffusing through intact human skin with: T_L*: lag time, e: thickness of the membrane,* D*: diffusion constant of the drug in the membrane.*

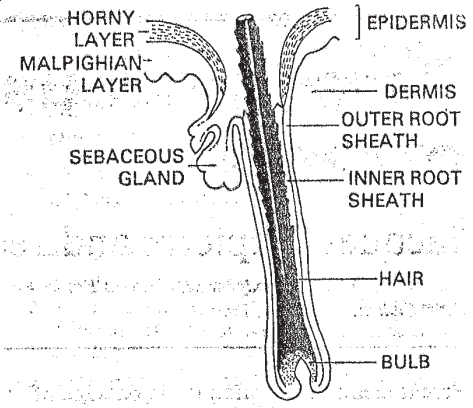

Fig. 4. Schematic structure of hair follicle. The outer root sheath is cornified like epidermis from the surface of skin to the opening of the excretory duct of sebaceous gland. In the inner part of the hair follicle, cell junctions of the outer and inner root sheaths are tight. In these conditions the sebaceous gland is the easiest route for diffusion.

is much more permeable than normal skin. Finally cutaneous irritation and *stratum corneum* stripping considerably increase the permeability of the skin. Systemic toxic effects have been reported after the application of various drugs on damaged skin (hexachlorophane).

Hydration of the stratum corneum. *In vivo,* the *stratum corneum* is partially hydrated[7]. Water coming from insensibile water loss penetrates the cells where it is trapped by water soluble substances included in cornified cells. Hydration may vary to a considerable extent, producing a rearrangement of the cellular constituents and decreasing their resistance to diffusion. Occlusive dressings are used in dermatology to increase absorption of corticosteroids which are normally poorly absorbed.

Parallel diffusion pathways – role of skin appendages

As the *stratum corneum* is only slightly permeable, it is possible to consider parallel paths for absorption, e.g. sweat glands and pilo-sebaceous apparatus.

If the sweat glands seem to have a negligible role, the pilo-sebaceous system has for a long time been considered as the main route for drug absorption. Easier diffusion pathways are located, as shown in Fig. 4, at the level of the sebaceous gland since the sebum is only found between the outer medium and the glandular acini.

The work of Tregear[8] and of Scheuplein and Blank[7] has shown that epidermis and appendageal diffusion are involved to a variable extent in the absorption of drugs. Skin appendages act as diffusion shunts alongside the slower route directly through the *stratum corneum*. In man, there are relatively few hair follicles and the frac-

tional area of the skin covered by appendages over most of the body is quite small. The absorption surface of hair follicles is 100 to 10,000 times less than that of the *stratum corneum*. The permeability of these shunts can be high, since the diffusion constant of the chemical substances through the *stratum corneum* is 100 to 10,000 times less than that through the sebaceous structures. For a given drug therefore, the penetration routes will mostly be a function of the value of the diffusion constants (Fig. 5). For the small, diffusible, non-electrolyte molecules (alcohols), the lag time is reduced for absorption across epidermis and hair follicles; it does not exceed more than a few minutes. The flux rapidly becomes constant by the two routes, which both participate in the absorption. The proportion of each one depends on the pilosity of the skin. For less diffusible molecules, such as various steroids, the lag times last several hours. Absorption occurs at first by the transfollicular route, then progessively also takes place at the epidermis level. Finally, for drugs with a very small diffusion constant through the *stratum corneum* (polar steroids), the lag time reaches several days and absorption occurs only via hair follicles.

Superficial and deep retention of drugs applied to the skin

Vickers[10] was the first to demonstrate the existence of a depot in the skin for topically applied agents (corticosteroids, griseofulvin, estradiol). This phenomenon called the 'reservoir effect' is a property

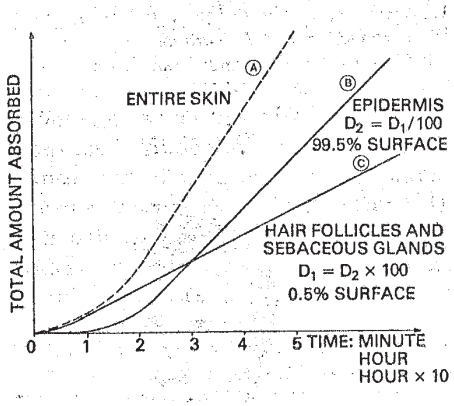

Fig. 5. Total amount of drug absorbed by the entire skin (A), by the epidermis (B) and by hair follicles (C). From this figure it can be seen that absorption by entire skin is the sum of absorption by the epidermis and hair follicle. It is supposed that the area of hair follicle represents 0.5% of the area of the epidermis. The diffusion constant through epidermis is 100 times lower than the diffusion constant through the hair follicles. At the steady state the flux by hair follicles is one-half the flux by the epidermis. The lag times depend on the constant of diffusion. They can vary from some minutes to several hours for

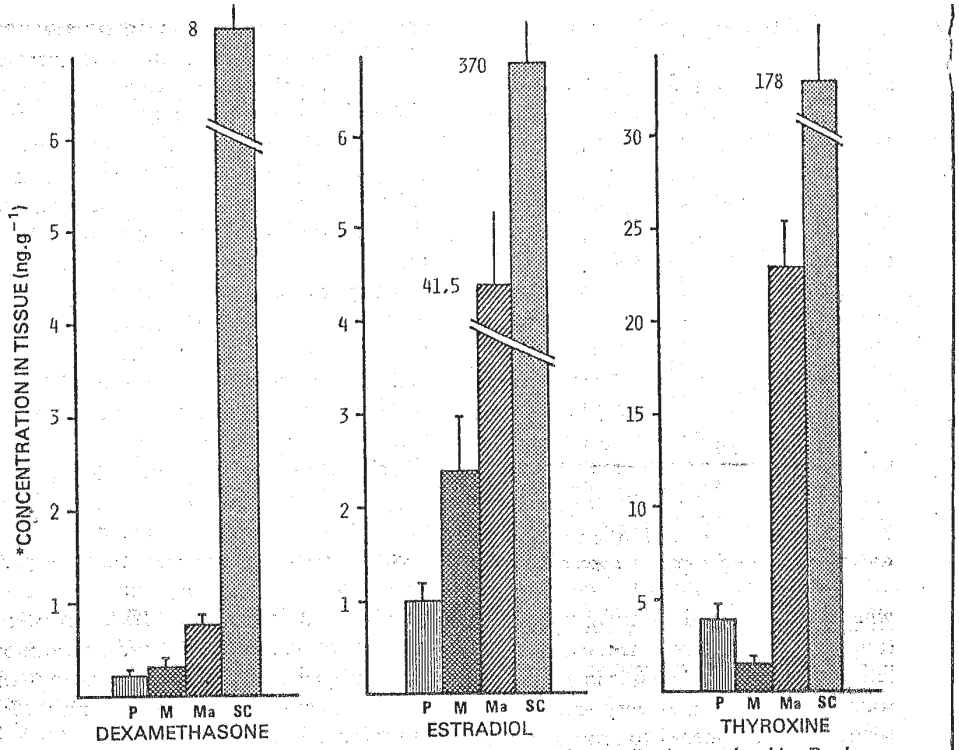

Fig. 6. Subcutaneous tissue retention of various drugs in the rat after application on the skin; P: plasma, M: muscle of the leg, Ma: muscle under surface of application of the drug, SC: tissue immediately under surface of application of the drug.

of the cornified cells. The molecules stored are partly slowly absorbed, over a period of ⩾7 days, and partly removed by repeated washing and skin contact. The reservoir effect can explain some characteristics of percutaneous therapy. A single application often leads to prolonged effects, and this is of significance not only for drugs designed for superficial effects (antiseptics, antibacterial agents, sunscreens), but also for those required for deep action. For the latter, retention is adequate only for drugs with high biological activity, since the storage capacity of the *stratum corneum*, whose volume is reduced, is small.

A transient concentration gradient[12] has also been shown in the deep parts of the skin and even in the subcutaneous connective tissue with, e.g. estradiol, thyroxin, corticosteroids, 8-methoxypsoralen (Fig. 6). This accumulation may be a consequence of the horny-layer reservoir effect. It appears when the bloodstream resorption rate is insufficient or when a binding of drug occurs on soluble macromolecules or cellular fractions of skin (corticosteroids). These phenomena tend to prove that the percutaneous route is available to obtain local effects in the depth of the skin without systemic action.

Excipient effect

The vehicles used in dermatology are able to modify percutaneous absorption of drugs in two ways: reversible physiological change in the properties of the *stratum corneum* (hydration) or change in the rate of release of the drug from the vehicle by modification of *stratum corneum*/vehicle partition coefficient.

Stratum corneum *hydration*

Percutaneous absorption is increased by vehicles such as petroleum jelly and oils, which form a waterproof film at the surface of the skin and prevent perspiration. Like water, aprotic solvents (dimethylsulphoxide) increase the penetration rate significantly and almost reversibly, but they are toxic and their use is limited[7].

Modification of the partition coefficient: stratum corneum/*vehicle*

The permeability constant is proportional to the *stratum corneum*/vehicle partition coefficient. This coefficient represents the relative affinity of the dissolved drug for the vehicle and for the *stratum corneum*[4,11]. When the coefficient is high, the drug easily leaves the vehicle for which it has a low affinity. This happens when it is slightly soluble. Conversely a small coefficient means a greater interaction between the solute and the vehicle. Based on these data, Blank[1] was able to show in a series of alcohols the importance of the affinity for the vehicle on the percutaneous bioavailability. Water-soluble ethanol has a higher permeability constant

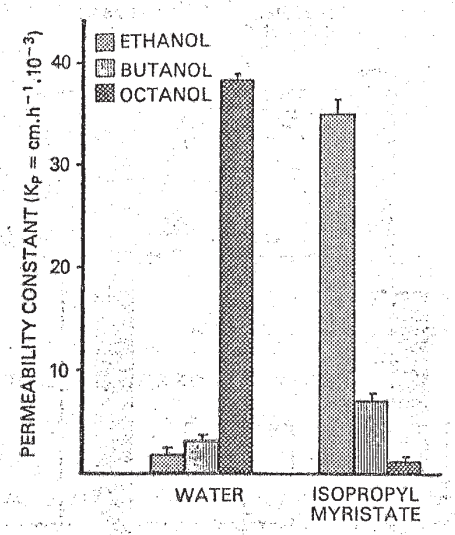

Fig. 7. Permeability constant of ethanol, butanol and octanol dissolved in water or isopropyl myristate.

when it is dissolved in an oily excipient (olive-oil, paraffin-oil), for which it has little affinity, than when it is in an aqueous solution in which it is very soluble, and where it has a tendency to remain. On the other hand, pentanol and octanol give a higher permeability constant when they are applied to the skin in an aqueous solution, where they have low solubility, than in an oily solution (Fig. 7). When the partition coefficient *stratum corneum*/vehicle is high, the drug is poorly soluble in the excipient. Under these conditions, in spite of a high permeability constant, the quantities actually absorbed, which are equal to the product of the permeability constant by concentration, remain small. Thus two factors act in opposite directions. Poulsen[6] has shown the optimal condition of liberation in the *stratum corneum* for corticosteroids incorporated in a water/propylene glycol mixture. The liberation is maximized by addition of a quantity of propylene glycol just sufficient to dissolve the corticosteroid at the concentration selected.

Surfactants, often included in pharmaceutical formulations, act on percutaneous absorption in two opposite manners[4,11]. (1) The irritant action increases permeability of the *stratum corneum* and absorption of drugs. This is the main effect observed with anionic and cationic surfactants. (2) Tensioactive agents increase solubility of drugs in the vehicle and in this way decrease *stratum corneum*/vehicle partition coefficient and permeability constant of the drug. This is the major action of non-ionic surfactants which have no irritant effect. The addition of surfactant seems to be the greatest when the drug is initially poorly soluble in the vehicle (Fig. 8).

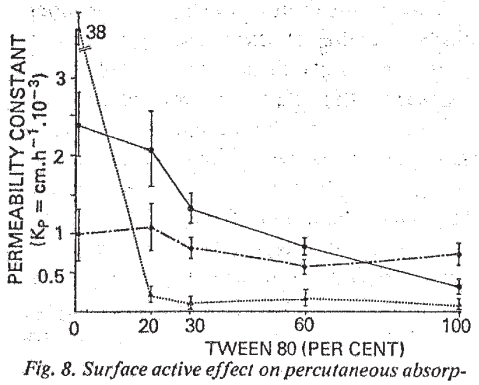

Fig. 8. Surface active effect on percutaneous absorption of drugs dissolved in a mixture water-Tween 80 –·–·–: ethanol ———: butanol – – –:

The role of emulsions, particularly with regard to oil in water (O/W) and water in oil (W/O) bases is the most difficult to predict. It seems, however, that the permeability constant depends, at least initially, on the partition coefficient between the *stratum corneum* and the continuous phase of the emulsion. Investigations of this aspect have been made with alcohols, estradiol and progesterone[11].

Conclusions

The application of drugs to the skin has been used for a long time to obtain surface effects or to develop a deep localized action. The interest in the latter is justified since we now know that many drugs are retained for a long time in the cutaneous and subcutaneous structures in the treated zone. One must remember that only normal skin is impermeable. Lesions, irritation and pathological states increase permeability of the skin. Its alteration can produce toxic effects when applying preparations designed for normal skin.

Until now, the percutaneous route has been little used to obtain systemic effects, because these effects appear only with powerful drugs. In addition this route lacks precision regarding the real dose absorbed. Finally it is necessary that delivery systems are non-irritant and non-sensitizing substances. In spite of these disadvantages the search for systemic effects can be justified: (1) for drugs which may be destroyed by enzymes in the digestive tract or trapped by the liver before they reach the systemic bloodstream (first pass effect); (2) to obtain long lasting effects.

Progress in our knowledge regarding the effect of vehicles and various absorption promoters on the percutaneous absorption of drugs should enable a wider use of this route, which is still often neglected.

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