**Rationale for the Production and Dermal Application of Lipid Vesicles**

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**Introduction**

Lipid vesicles, liposomes, have received much attention over the past few years in the field of topical dermal applications [7, 17, 19]. To date, however, mainly the formulations of standard lipid vesicles were used for this purpose, and little extra concern has been given to the special constraints and opportunities of the drug targeting to skin.

The time thus is ripe for the optimization of the lipoidal carriers for dermal use since many of the non-optimal formulations are likely to cause unnecessary side effects and also leave certain therapeutic opportunities unexploited. As a starting point for this task, a discussion of the fundamental rules and considerations for the development and use of lipoidal drug carriers in dermatology is given in this contribution. On the one hand, attention is paid to the special properties and anatomy of mammalian skin; this affects significantly the mode and path of the particulate dermatics action. On the other hand, some implications of the concept of rational membrane design, recently introduced and developed in our laboratory, are discussed with special concern being given to the mechanism of carrier penetration into intact skin.

**Skin as a Target and Application Site**

The outer skin region, or epidermis, in humans is normally around 30 µm and, very seldom, up to 4 mm thick [11, 18]. Its outer, horny part or stratum corneum consists of some 20 keratinized layers of flattened, largely dead cells. The narrow interstices between these corneocyte cells are filled nearly completely with quasi-lamellar structures consisting of approximately 80%, chiefly saturated, lipids; the corneocyte interior is filled by the keratin filaments, by and large. The stratum corneum, consequently, is mechanically very rigid and acid-resistant. It is poorly permeable to water and aqueous solutions and also an efficient permeability barrier for lipophilic substances [10, 12, 18]. The stratum corneum thus prevents both a significant loss of the body fluids, lipids, and macromolecules from the skin depth, as well as the counterdirected transport of the superficially applied agents into the deep skin strata.
The sub-epidermal skin region is called the dermis or corium and is 10–20-times thicker than the epidermis. The dermis shelters blood capillaries, certain glands, immunologically active cells, nerve endings, etc. This region thus is often a preferred site for the dermatological drug delivery. But the stratum corneum per se is seldom a goal of therapeutic drug applications, except when certain fungal and bacterial infections are to be eradicated. It is just the first compartment into which and through which a drug molecule or its carrier must penetrate in order to reach their final destination after a non-invasive dermal application. The reasons for the impermeability of the epidermal layer and various possibilities for its circumvention, therefore, should be understood before a therapeutically successful solution – with or without liposomes – is sought.

The only common answer to the problem of skin impermeability to date is to use skin penetration enhancers [6, 15]. Some of these are believed to increase the fluidity of and the spacings between the lipid lamellae in the stratum corneum; others have been inferred to interact with skin proteins and thus weaken the biopolymeric networks in the epidermis. The former should decrease the skin permeability barrier for small lipidic drugs, by and large; the latter should chiefly improve the skin permeability for small water-soluble drugs. Lipid vesicles, which are large entities, are likely to act by another mechanism (see further below). Nevertheless, the kinetics and the average diffusion path of both drug carrier as well as agent molecules must always be considered simultaneously in order to ensure an optimal distribution and activity of the applied drugs in the intact skin. This aspect has seldom been given due attention in the dermal liposome applications.

**Drug Distribution**

After parenteral application, any set of drug molecules or carriers, at least initially, is distributed relatively uniformly throughout the whole body via the blood circulation [9]. After a topical, such as dermal, application, the situation is different. The use of carriers and drugs with an intrinsic capability and tendency to distribute throughout the target region is thus of paramount importance for the prevention of large intra- or trans-dermal drug concentration gradients.

Amphiphilic agents with a high water and lipid solubility, therefore, are optimally suited for topical application by using liposomes. Once such molecules have been brought in the vicinity of a target site, with the aid of a lipid vesicle, for example, their diffusion is only little hindered by the intermediate aqueous or fatty compartments, such drug molecules being partly soluble in both. Amphiphilic molecules thus have a reasonably high propensity for a rapid and fairly homogeneous redistribution in most composite lipid-water systems over distances in the order of several micrometers; this typically requires no more than an hour of equilibration time (Fig. 1. middle panel).