

Formulating for Efficacy

Johann W. Wiechers

Uniqema Skin R&D, Gouda, The Netherlands

Caroline L. Kelly and Trevor G. Blease

Uniqema R&D Department, Redcar, United Kingdom

J. Chris Dederen

*Uniqema Personal Care Applied Research and Technical Service Group,
Redcar, United Kingdom*

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ABSTRACT: *Via the introduction of the Relative Polarity Index, the authors show that the choice of emollients in cosmetic formulations determines the total amount of skin penetration of active ingredients whereas the choice of the emulsifier determines its distribution within the skin.*

Active ingredients have been popular for more than a decade, and new actives are continuously being identified, studied and promoted. Many of these are supported by good in vitro efficacy data, and there is an increasing number of ingredients for which also good in vivo efficacy evidence is available.

Based on this, one would expect to find many active cosmetic products in the marketplace, but unfortunately this is not the case. Assuming that the efficacy data provided is robust (i.e., the active ingredient has indeed its claimed cosmetic activity), questions arise about the formulation development process that should assure that the efficacy of an active ingredient is transformed to an efficacious cosmetic product. Cosmetic formulators should therefore select their ingredients and manufacturing procedures in such a way that

cosmetic efficacy is obtained. In other words, they should formulate for efficacy. In many cases, however, this does not happen.

Many companies have a number of standard formulations to which the latest new active ingredient is simply added. Following stability testing and elimination of those failing the stability tests, small clinical trials are performed with the remaining formulations to assess whether the claimed efficacy of the active ingredient is maintained in the standard formulation. In most cases, no efficacy is seen and after some additional work, the active ingredient is discarded. Whereas the reasons for using standard formulations are very understandable, this strategy does not lead to the best possible product because it completely ignores the principles that underpin the skin delivery of the active ingredient.

This chapter describes the selection criteria for ingredients in cosmetic formulations that help to optimize the delivery of the active ingredient into the skin. As formulations can be very complicated, many factors need to be taken into account. To date only a few have been systematically studied. The guidelines described in this chapter are, therefore, only guidelines but the guideline recipe will be a lot closer to an efficacious cosmetic formulation than a random choice from a selection of standard formulations. As further results from new work become available, the system will be further refined.

Theoretical Considerations for the Skin Delivery of Cosmetics

As illustrated in **Figure 1**, Barry described the skin penetration process as a series of consecutive steps, each of which can potentially be rate limiting.¹ First, the chemical needs to diffuse within the formulation to the skin surface. There it partitions into the skin, diffuses through the stratum corneum, partitions into the viable epidermis and diffuses through the viable epidermis. It then partitions into and diffuses through the dermis before partitioning into the fat deposits or it partitions into the blood capillaries just beneath the viable epidermis/dermis interface.

From this, it can be concluded that both partition and diffusion are very important in determining skin penetration. They are

normally combined in the permeability coefficient according to the formula:

$$k_p = \frac{K_{oct/water} \cdot D}{L} \quad (\text{Eq. 1})$$

in which k_p is the permeability coefficient, $K_{oct/water}$ the octanol/water partition coefficient, D the diffusion coefficient and L the length of the pathway of diffusion of the penetrating molecule. The unit of the permeability coefficient, cm/s, indicates that this parameter basically reflects the speed with which a chemical diffuses through the stratum corneum. However, in order to obtain efficacy a sufficiently high concentration of the active ingredient needs to be reached at the site of action and maintained for a sufficiently long period of time. Absolute amounts are therefore also important but here some conflicting evidence is obtained from skin penetration theory.

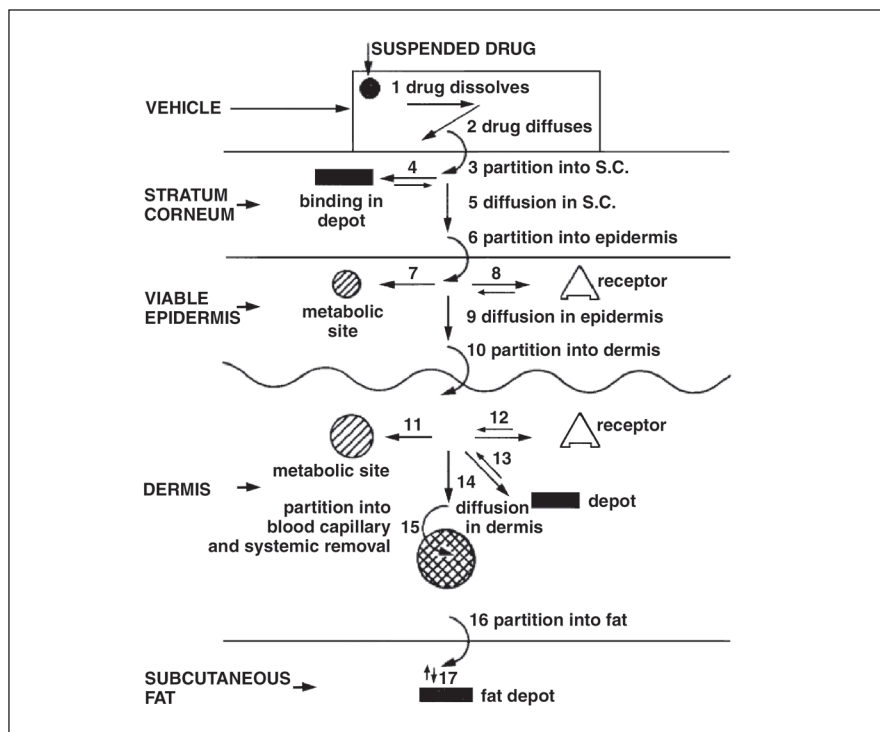


Figure 1. The various subsequent steps that an active ingredient will have to undertake during its journey from the formulation in which it is incorporated to its site of action. Reproduced with the permission of the author and Marcel Dekker Inc., New York, NY, USA.

The most logical way to increase the degree of skin penetration is to increase the concentration of the active ingredient in the formulation, according to the well-known formula:

$$J = k_p \cdot \Delta C = \frac{K \cdot D}{L} \cdot \Delta C \quad (\text{Eq. 2})$$

in which ΔC is the concentration difference of the penetrating molecule over the stratum corneum, i.e., the difference in concentrations between the formulation and the deepest layers of the stratum corneum. The larger this concentration difference, the greater the flux through the stratum corneum. At the same time, the more soluble an active ingredient is in the formulation, the more active ingredient can be contained in the formulation and the more can therefore penetrate into the stratum corneum.

But difficulties arise when increasing the solubility of the active ingredient in the formulation. According to the definition of the partition coefficient, the $K_{\text{sc/form}}$ of the penetrating molecule, the solubility of the active ingredient in the stratum corneum is related to its solubility in the formulation as expressed in **Equation 3**:

$$K_{\text{sc/formulation}} = \frac{C^{\text{penetrant}} \text{ in stratum corneum}}{C^{\text{penetrant}} \text{ in formulation}} \quad (\text{Eq. 3})$$

in which $C^{\text{penetrant}}$ represents the solubility of the penetrating molecule in either the stratum corneum or the formulation. Because this K is the same as those in **Equations 1** and **2**, the quantity of penetrating molecules into the stratum corneum can be increased by increasing the solubility of the penetrating molecule in the stratum corneum or by reducing its solubility in the formulation. One therefore needs to increase the solubility of the active ingredient in the formulation in **Equation 2** to achieve sufficiently high quantities to obtain efficacy in the skin, but one needs to reduce the same solubility in order to force the material to leave the formulation and partition into the stratum corneum.

The remainder of this chapter will describe how can one increase and reduce the solubility of the active ingredient in the formulation