Formulating for Efficacy

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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 article 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 article 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:

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

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

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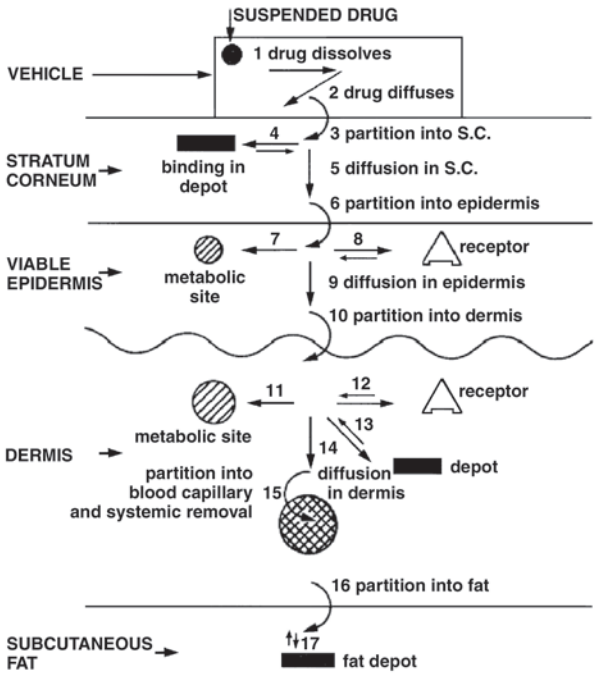

Figure 1. The various subsequent steps that an active ingredient will have to undertake during its journey from the formulation in which it is incorporated to its site of action. Reproduced with the permission of the author and Marcel Dekker Inc., New York, NY, USA.

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.

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:

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

in which ΔC 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 $K_{sc/form}$ 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:

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

in which $C^{penetrant}$ represents the solubility of the penetrat-ing 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 article will describe how can one increase and reduce the solubility of the active ingredient in the formulation at the same time via formulation design using the Relative Polarity Index (RPI).

The Influence of Formulation Characteristics on Skin Delivery

The theoretical discussion above clearly indicates that the formulation determines the following parameters:

- The total amount dissolved in the formulation that is available for skin penetration; the higher this amount, the more will penetrate until a saturation concentration is reached in the skin, therefore a high solubility in the formulation is required.
- The polarity of the formulation relative to that of the stratum corneum; if a penetrant dissolves better in the stratum corneum than in the formulation, then the partition of the active ingredient will favor the stratum corneum, therefore a low solubility in the formulation is required.

Both requirements cannot be fully met at the same time but the problem can still be solved using the novel concept of a Relative Polarity Index (RPI). In this systematic approach, it is essential to consider the stratum corneum as yet another solvent with its own polarity.

It appears that the stratum corneum behaves very similar to butanol, but in a somewhat more polar fashion than butanol with respect to its solubilizing ability for penetrants.[2] The experimentally determined log $K_{octanol/water}$ of 1-butanol is 0.88.[3] For the purpose of this work, the polarity

of the stratum corneum as expressed by its octanol/water partition coefficient is set at $10^{0.8}$, which is 6.3.

Partition Coefficient Determination or Calculation

For the following, it is essential to know what an octanol/water partition coefficient is. The octanol/water partition coefficient is calculated according to the formula:

$$K_{octanol/water} = \frac{C_{max}^{penetrant}\ in\ octanol}{C_{max}^{penetrant}\ in\ water} = \frac{C^{penetrant}\ in\ octanol}{C^{penetrant}\ in\ water} \quad \text{(Eq. 4)}$$

n-Octanol and water do not mix and the octanol/water partition coefficient is a measure of the polarity of a chemical. If the chemical is lipophilic, larger amounts will dissolve in the lipophilic *n*-octanol than the polar water. For a hydrophilic chemical, this will be reversed.

This coefficient can be experimentally determined by assessing the maximum solubility of a chemical in *n*-octanol and in water, respectively, or by assessing the ratio of the concentrations of the chemical when dissolved in both phases at levels below the maximum solubility. Alternatively, the partition coefficient can be estimated from the chemical structure, although care should be taken which method of calculation is being used.[4] One should realize that the partition coefficient is often expressed by its logarithmic value; in this article the RPI value of a chemical, stratum corneum or formulation is the ^{10}log of the corresponding octanol/water partition coefficient.

The Relative Polarity Index

The Relative Polarity Index (RPI) is a way to compare the polarity of an active ingredient with that of the skin and emollient components of cosmetic formulations. It is visualized as a vertical line with a high polarity at the top and a high lipophilicity at the bottom. The polarity is expressed by the octanol/water coefficient. In order to use the concept of the Relative Polarity Index, three numbers (on $\log_{10}$ scale) are required, namely:

- The polarity of the stratum corneum, here set at 0.8 (but in reality this value will change with the hydration state of the stratum corneum that is determined by factors such as the external relative humidity);[5]
- The polarity of the penetrating molecule;
- The polarity of the formulation. For multiphase (i.e., multi-polarity) systems like emulsions, this is the phase in which the active ingredient is dissolved.

The polarities of these three entities can be placed on the RPI by simply marking their position on the vertical line.

Case I: Penetrants with a polarity equal to the stratum corneum: Imagine the example of an active ingredient with a log $K_{oct/water}$ equal to that of the stratum corneum (0.8). If the formulation now also has the same polarity, the solubility of the penetrant in the stratum corneum and the formulation would be the same. After equilibrium is reached, the concentration of active ingredient over the two phases (formulation and stratum corneum) would be the same although the absolute amount in both layers will depend on their respective volumes.

Based on the physicochemical characteristics of the system, there is no drive for the active ingredient to leave the formulation and enter the skin, apart from the fact that the stratum corneum does initially not contain any penetrant

(i.e., a dilution effect). Such a situation is very unlikely because in reality almost all active ingredients have polarities that differ from that of the stratum corneum. The second and third case are therefore much more common and deserve separate discussion.

Case II: Penetrants more polar than the stratum corneum: In order to illustrate the use of the RPI with a penetrant that is more polar than the stratum corneum, it is assumed that the active ingredient is the skin whitener arbutin with a calculated log $K_{octanol/water}$ of 0.01. First, the polarity difference between the stratum corneum and the penetrant is calculated by subtracting the polarity of the penetrant from that of the stratum corneum; in this case 0.8 – 0.01 = 0.79. See Figure 2

In the second step, the polarity of the formulation is calculated. The polarity of the phase of the formulation in which the active ingredient is dissolved should be 0.79 more or less than that of the active ingredient itself; that means either greater than 0.8 (0.01 + 0.79) or smaller than –0.78 (0.01 – 0.79).

For formulations that are more lipophilic than the stratum corneum, the arbutin will be more soluble in the stratum corneum than in the formulation and would therefore prefer to be located in the stratum corneum, creating a driving force for partitioning into the stratum corneum. The more extreme the difference in polarity between the formulation and the active ingredient, the greater this driving force for partition into the stratum corneum. This is illustrated on the left in Figure 3 by the width of the red blocks (arrows).

However, at the same time, the solubility of the penetrant in the formulation will reduce if the polarity difference between formulation and active ingredient is enlarged. This is illustrated by the green blocks on the right in Figure 3.

In the case of arbutin, a formulation with a polarity of 4 has a greater driving force for partitioning arbutin into the stratum corneum than a formulation with a polarity of 1 because 3.99 (4 – 0.01) is greater than 0.99 (1 – 0.01). Likewise, a formulation with a polarity of –3 has a greater driving force for partitioning arbutin into the stratum corneum than a formulation with a polarity of –1 because 3.01 (–3 – 0.01) is greater than 1.01 (–1 – 0.01). Only the absolute difference counts. Practically, of course, it is much more difficult to dissolve arbutin in an aqueous solvent with a polarity of –3 than –1 or a lipophilic solvent with a polarity of 4 than 1.

Case III: Penetrants more lipophilic than the stratum corneum: A much more common situation is that in which the penetrants are more lipophilic than the stratum corneum. This time, it is assumed that the active ingredient is octadecenedioic acid (referred to hereafter as dioic acid), a much more lipophilic skin whitener[6] with a theoretical log $K_{octanol/water}$ of 5.84 and an experimentally determined log $K_{octanol/water}$ of 5.74 ± 0.29. For simplicity, the value of 5.8 has been used in the calculations. Again, the polarity difference between the stratum corneum and the active ingredient needs to be calculated first, which is 5 (5.8 – 0.8). See Figure 4.

In the next step, the polarity of the formulation should be calculated. The polarity of the phase of the formulation in which the active ingredient is dissolved should be more than 5 away from that of the active ingredient itself; that is, either above 10.8 (5.8 + 5) or below 0.8 (5.8 – 5).

For formulations that are less lipophilic than the stratum corneum, the dioic acid is more soluble in the stratum

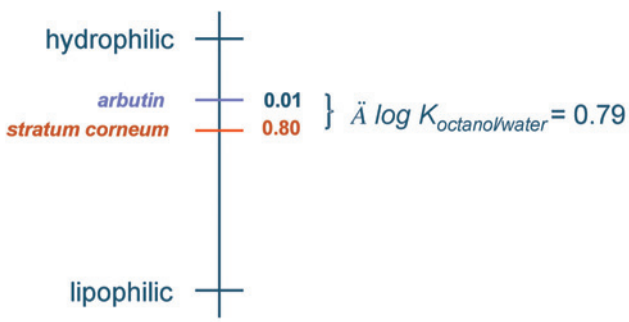

Figure 2. Visualization of the penetrant polarity gap between an active ingredient more polar than the stratum corneum (in this case arbutin) and the stratum corneum using the Relative Polarity Index

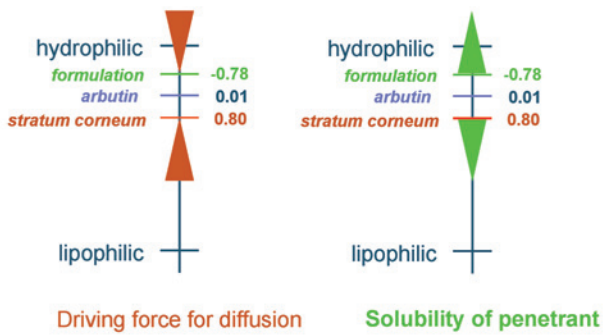

Figure 3. Example of the calculation of the polarity of a formulation for penetrants more polar than the stratum corneum. Arbutin is used as an example. On the left, the influence of the polarity of the formulation on the driving force on diffusion is illustrated and on the right, the influence of the polarity of the formulation on the solubility of the penetrant is illustrated.

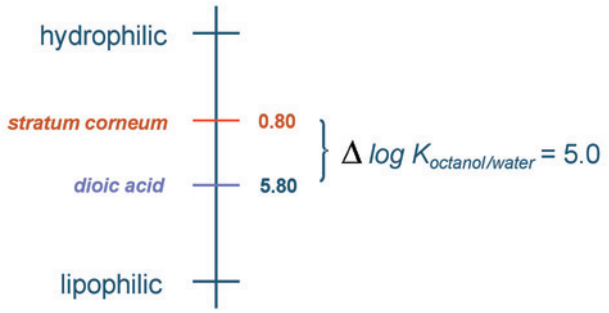

Figure 4. Visualization of the polarity gap between an active ingredient more lipophilic than the stratum corneum (in this case octadecenedioic acid) and the stratum corneum using the Relative Polarity Index

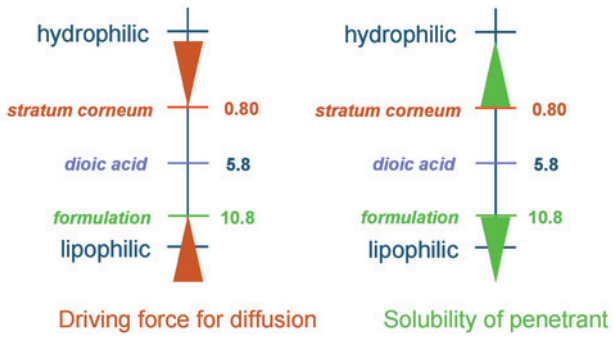

Figure 5. Example of the calculation of the polarity of a formulation for penetrants more lipophilic than the stratum corneum. Octadecenedioic acid is used as an example. On the left, the influence of polarity of the formulation on the driving force on the diffusion is illustrated and on the right, the influence of the polarity of the formulation on the solubility of the penetrant is illustrated.

corneum than in the formulation and would therefore 'prefer' to be located in the stratum corneum rather than in the formulation, creating a driving force for partition into the stratum corneum. As before, the more extreme the difference in polarity between the formulation and the active ingredient, the greater the driving force for partition into the stratum corneum. This is illustrated on the left in Figure 5.

At the same time, the solubility of the penetrant in the formulation will reduce if the polarity difference between formulation and active ingredient is enlarged. This is illustrated on the right in Figure 5.

In the case of dioic acid, a formulation with a polarity of 10 has a greater driving force for partitioning dioic acid into the stratum corneum than a formulation with a polarity of 7 because 4.2 (10 – 5.8) is greater than 1.2 (7 – 5.8). Likewise, a formulation with a polarity of –3 has a greater driving force for partitioning dioic acid into the stratum corneum than a formulation with a polarity of –1 because 8.8 (–3 – 5.8) is greater than 6.8 (–1 – 5.8). Again, only the absolute difference counts. Practically, of course, it is much more difficult to dissolve dioic acid in an aqueous solvent with a polarity of –3 than –1 or a lipophilic solvent with a polarity of 10 than 7.

Using the Relative Polarity Index in Practice

From the theory discussed above, it can be concluded that the polarity of the formulation needs to be as far away as possible from the polarity of the active ingredient in order to increase the driving force of the active ingredient into the skin, but at the same time as close as possible to that of the active ingredient to ensure that high concentrations can be reached to ensure that enough material penetrates. Because these two opposing requirements cannot be met at the same time, it is necessary to describe how to find the optimum polarity of the formulation from the point of view of skin delivery.

Step 1: Optimizing the solubility by selecting the primary emollient or solvent: After having calculated the polarity difference between penetrant and stratum corneum and hence the acceptable polarity ranges of the formulation, the formulator should have an idea whether the phase containing the active ingredient will be hydrophilic or lipophilic in nature. In other words, will the formulation be at the top or at the bottom of the RPI as indicated by the arrows in Figures 3 and 5? It is important to note that if a lipophilic penetrant is dosed in an o/w emulsion and dissolved in the internal oil phase, the phase containing the penetrant is lipophilic in nature whereas the formulation may be hydrophilic in nature.

As a first step, an emollient (for lipophilic active ingredients) or a water-miscible solvent (for hydrophilic active ingredients) in which the active ingredient dissolves well should be identified. This primary emollient or solvent is chosen in the direction of the required RPI. In other words, choose an emollient with a RPI value not too far away from that of the active ingredient, for instance 7 or 8 in case of dioic acid if the polarity of the final formulation will be lipophilic or 3 or 4, if the final formulation will be hydrophilic. Table 1 provides RPI values of some typical emollients and hydrophilic solvents that span a wide range. These RPI values can be used to select a suitable solvent or emollient.

Step 2: Optimizing the driving force by selecting the secondary emollient or solvent: Once a suitable primary

emollient or solvent has been selected, the driving force for penetration into skin needs to be increased by reducing the solubility in that solvent. This is typically done by incorporating another solvent, the secondary emollient or solvent, in which the active ingredient is far less soluble but still miscible with the originally chosen solvent or emollient.

When adding increasing amounts of the secondary emollient or solvent, the solubility of the active ingredient is gradually reduced and, as a consequence, the total amount of active ingredient dissolved relative to what could be dissolved increases. Sufficient secondary emollient or solvent has been added when this fraction of maximum solubility has reached a value of about 90% in that solvent mixture.

Skin Delivery Experiments Demonstrating Use of RPI

An example of the use of RPI is the formulation of dioic acid for which RPI values of more than 10.8 and less than 0.8 would be acceptable.

Propylene glycol isostearate with an RPI of 6.08 was chosen as the solvent for this particular penetrant and the solubility assessed to be 17% w/w. This solubility was too high to guarantee a good driving force for diffusion; therefore, increasing amounts of triethylhexanoin were added to reduce the solubility to just above 2% in the total formulation (10% in the oil phase). In this way, the composition shown in Formula 1 was created. Formula 2 was made simply based on

Table 1. Relative Polarity Index values for some hydrophilic solvents and lipophilic emollients typically used in cosmetic formulations

INCI name	Trade name, supplier	Calculated log P value
Glycerin	Pricerine 9091, Uniqema	-1.76
Dipropyleneglycol	DPG LO+, Dow Chemical USA	-1.20
Propylene glycol	1,2-Propylene Glycol Care, BASF	-0.92
Ethanol	Pharconix BPS PF, Ichimaru Pharcos.	-0.32
Triethylhexanoin	Estol 3609, Uniqema	2.70
Glyceryl isostearate	Prisorine 2040, Uniqema	4.76
Isopropyl myristate	Estol 1512, Uniqema	5.41
Propylene glycol isostearate	Prisorine 2034, Uniqema	6.08
Isopropyl isostearate	Prisorine 2021, Uniqema	7.40
Ethylhexyl palmitate	Estol 1543, Uniqema	9.12
Ethylhexyl isostearate	Prisorine 2036, Uniqema	10.05
Vegetable squalane	Pripure 3759, Uniqema	14.93
Triisostearin	Prisorine 2041, Uniqema	18.60
Trimethylolpropane triisostearate	Prisorine 3630, Uniqema	20.27
Pentaerythrityl tetraisostearate	Prisorine 3631, Uniqema	25.34
Isostearyl isostearate	Prisorine 2039, Uniqema	26.98

physical stability of the emulsion system. Formulas 1 and 2 were used to demonstrate the influence of the emollients on skin delivery. Formula 3, which differed from Formula 1 principally in the choice of surfactants, was used to investigate the influence of the emulsifier on skin delivery.

The influence of the emollients: Formulas 1 and 2 were tested separately for skin delivery.

For the delivery-optimized formulation (Formula 1), full-thickness pigskin dermatomed to 400 µm was used in vitro in a Franz-diffusion cell dosed at a rate of 10 µL/cm². Cells were left in place for 24 hours after which the formulation was removed; the skin was tape-stripped 21 times; strips, remainder of skin and receptor fluid were analyzed to assess skin penetration.

For the formulation that was not optimized for skin delivery (Formula 2), full-thickness pigskin (500 µm) was used in vitro in a Bronaugh flow-through diffusion cell dosed at a rate of 66 µL/cm². Cells were left in place for 20 hours after which the formulation was removed; the skin was tape-stripped 5 times; strips, remainder of skin and receptor fluid were analyzed to assess skin penetration. Results of these experiments are given in Figure 6.

As can be seen from Figure 6, the total delivery (i.e., the sum of the amounts recovered in the tapes, the skin and transdermal delivery) is far greater from the formulation that was optimized for skin delivery, therefore illustrating the validity of the use of RPI values for selecting emollients to enhance skin delivery.

The differences in skin penetration methodologies between the two experiments were only minor; although the delivery-optimized formulation had a 6-fold lower dosing rate than the formulation not optimized for skin delivery (favoring the skin penetration from the latter), both were performed under infinite dosing conditions. Dermal delivery after 22 hours may be considered to be constant after steady-state transdermal fluxes have been achieved (data not shown). In other words, we believe the observed difference in skin penetration to be due to differences in formulation design rather than to differences in skin penetration methodology.

Because dioic acid needs to be delivered to the melanocytes where it reduces the quantity and/or half-life of the tyrosinase enzyme (the enzyme involved in skin color formation),[7] the delivery to the skin layer should be as high as possible. Due to the use of the RPI concept, the skin delivery has increased 3.5-fold, from 4.3 to 14.0 µg/cm², without an increase in the concentration of the active ingredient in the formulation.

Concentrations of above 2% dioic acid in the formulation that was not optimized for skin delivery were previously tested for skin delivery[8] and demonstrated that a 4-fold increase in dioic acid concentration in the formulation (from 2 to 8%) resulted in only a 2-fold increase of skin delivery (from 4.3 to

Formula 1. Dioic acid-containing o/w formulation designed according to the Relative Polarity Index principles, i.e. skin delivery optimized

Propylene glycol isostearate (Prisorine 2034, Uniqema)	15.0% w/w
Triethylhexanoin (Estol 3609, Uniqema)	3.0
Octadecenedioic acid (Arlatone Dioic DCA, Uniqema)	2.0
Steareth-21 (Brij 721, Uniqema)	5.0
Steareth-2 (Brij 72, Uniqema)	1.0
Glycerin (Pricerine 9091, Uniqema)	4.0
Xanthan gum (Keltrol, Kelco)	0.2
Phenoxyethanol (and) methylparaben (and) propylparaben (and) 2-bromo-2-nitropropane-1,3-diol (Nipaguard BPX, Nipa)	0.7
Aqua (water)	qs 100.0

Formula 2. Dioic acid-containing o/w formulation designed solely on physicochemical stability and not optimized for skin delivery

Caprylic/Capric triglyceride (Estol 3603, Uniqema)	10.0%w/w
Glyceryl stearate SE (Estol 1461, Uniqema)	3.0
Steareth-21 (Brij 721, Uniqema)	5.0
Steareth-2 (Brij 72, Uniqema)	1.0
Cetyl alcohol (Lanol C, Seppic)	2.0
Octadecenedioic acid (Arlatone Dioic DCA, Uniqema)	2.0
Glycerin (Pricerine 9091, Uniqema)	3.0
Benzoic acid (Unisept BZA, Universal Preserv-A-Chem Inc.)	0.2
2-Amino-2-methyl-1-propanol (AMP, Angus Chemie GmbH), to pH 5.5	qs
Aqua, distilled	qs 100.0

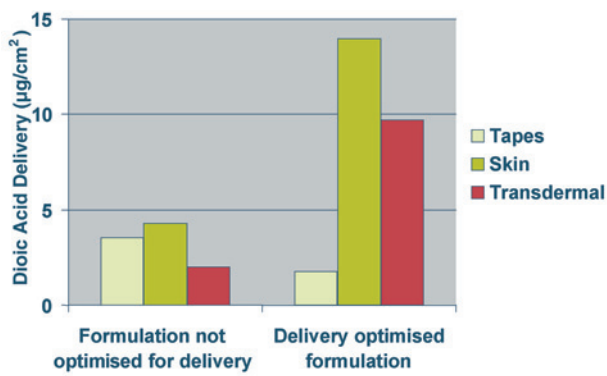

Figure 6. Skin delivery of octadecenedioic acid of a formulation not optimized for skin delivery and a delivery optimized formulation according to the Relative Polarity Index concept (for composition, see Formula 2 and 1, respectively). Note that the latter delivers significantly more dioic acid to the skin.

8.0 µg/cm²). It may therefore be advisable to change a standard formulation by selecting emollients according to the RPI concept rather than change the active ingredient or its concentration.

The influence of the emulsifier: So far, the tested formulations only differed in terms of their emollients, which showed that the choice of the emollients greatly influences the total quantity of active ingredient absorbed into the skin. But the effect of the emulsifier on skin delivery of active ingredients is also of interest. Emulsifiers often act as skin penetration enhancers, in particular the cationic, followed by the anionic and finally the nonionic. Whereas the nonionic surfactants penetrate better into skin, their interaction with skin lipids and therefore skin penetration enhancement is less extensive.[9]

In order to investigate the effect of the emulsifier on the skin penetration of dioic acid, Formula 3 was prepared using the same concentrations of dioic acid, propylene glycol isostearate and triethylhexanoin as in the skin delivery-optimized formulation, but a different surfactant was selected. Because this emollient combination was selected on the RPI concept, this is also a skin delivery optimized formulation. The only difference from the Formula 1 is the emulsifier system.

Skin delivery results are depicted in Figure 7 and show that while the total amount delivered is high in both cases (due to the choice of primary and secondary emollient via the RPI concept) a completely different skin distribution pattern is obtained. Because this has been observed a few times for different emulsifiers, both o/w and w/o, it is suggested that the emulsifier influences the distribution of the active ingredient within the skin. No explanation can be given for this phenomenon at the present time.

Formula 3. Dioic acid-containing o/w formulation designed according to the Relative Polarity Index principles using a different emulsifier system than Formula 1

Propylene glycol isostearate (Prisorine 2034, Uniqema)	15.0%w/w
Triethylhexanoin (Estol 3609, Uniqema)	3.0
Octadecenedioic acid (Arlatone Dioic DCA, Uniqema)	2.0
Sorbitan stearate (and) sucrose cocoate (Arlatone 2121, Uniqema)	5.5
Glycerin (Pricerine 9091, Uniqema)	4.0
Xanthan gum (Keltrol, Kelco)	0.2
Phenoxyethanol (and) methylparaben (and) propylparaben (and) 2-bromo-2-nitropropane-1,3-diol (Nipaguard BPX, Nipa)	0.7
Aqua (water)	qs 100.0

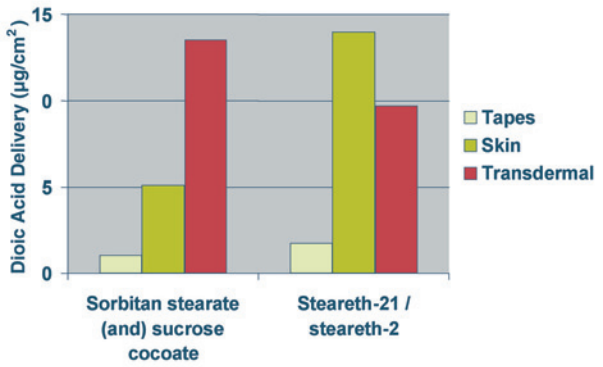

Figure 7. Skin penetration results of two almost identical formulations, only differing in their emulsifier system. Full composition details of the steareth-2/steareth-21 formulation are given in Formula 1 and that of the sorbitan stearate (and) sucrose cocoate formulation in Formula 3. Note that whereas the total amount delivered is high in both cases (as determined by the choice of the emollient(s)), the distribution profile of octadecenedioic acid is highly influenced by the choice of the emulsifier.

Conclusions

Most cosmetic companies will formulate their active ingredients into a few standard formulations prior to efficacy testing, almost exclusively based on physical and chemical stability and sometimes on sensory properties. Subsequent efficacy tests often reveal the cosmetic product to be without cosmetic activity.

Based on theoretical considerations, it was predicted that the polarity of the phase in which the active ingredient of a cosmetic formulation is located would have a profound influence on the flux of the active ingredient into the skin. Examples for a hydrophilic and a lipophilic penetrant clearly demonstrate that the efficacy of formulations can be improved by selecting the right emollient (system) using the Relative Polarity Index. This involves dissolving an active ingredient at the highest possible concentration in a primary emollient and then reducing its solubility to an acceptable level using a secondary emollient.

Initial skin penetration experiments showed that formulations designed according to this concept deliver significantly more active ingredient into the skin than formulations that have "only" been optimized for physical stability.

Further research into the other components of cosmetic formulations revealed that the choice of emulsifier is also important, because it seems to determine the distribution profile of the active ingredient within the skin. Whereas the reasons for the choice of the emollient are clearly understood from a theoretical point of view, the rationale for selecting

the right emulsifier remains unclear and further research will be necessary to elucidate the exact influence of the emulsifier on skin delivery.

References

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1. BW Barry, *Dermatological Formulations*, New York: Marcel Dekker (1983) p 128
2. RJ Scheuplein and IH Blank, Mechanism of percutaneous absorption. IV. Penetration of non-electrolytes (alcohols) from aqueous solutions and from pure liquids, *J Invest Dermatol* 60 286-296 (1973)
3. C Hansch and A Leo, *Substituent Constants for Correlation Analysis in Chemistry and Biology*, New York: J Wiley & Sons (1979)
4. R Mannhold, RF Rekker, C Sonntag, AM ter Laak, K Dross and EE Polymeropoulos, Comparative evaluation of the predictive power of calculation procedures for molecular lipophilicity, *J Pharm Sci* 84 1410-1419 (1995)
5. JA Bouwstra, A De Graaff, GS Gooris, J Nijsse, JW Wiechers and AC Van Aelst, Water distribution and related morphology in human stratum corneum at different hydration levels, *J Invest Dermatol* 120 750-758 (2003)
6. JW Wiechers, FJ Groenhof, VAL Wortel, NA Hindle and RM Miller, Efficacy studies using octadecenedioic acid, a new nature-derived ingredient to even Asian skin tone, *SÖFW* 128 2-8 (Sep 2002)
7. JW Wiechers, Melanosomes, melanocytes and dioic acid, Proceedings of the 37th Annual Conference of the Australian Society of Cosmetic Chemists, "Cosmetics on a New Horizon", 13-16 March 2003, Hamilton Island, Queensland, Australia
8. JW Wiechers, FJ Groenhof, VAL Wortel, RM Miller, NA Hindle and A Drewitt-Barlow, Octadecenedioic acid for a more even skin tone, *Cosmet Toil* 117(7) 55-68 (2002)
9. SB Ruddy, Surfactants, In *Percutaneous Penetration Enhancers*, EW Smith and HI Maibach, eds, Boca Raton: CRC Press (1995) pp 245-257

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