Formulating for efficacy

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Summary

Active ingredients have been around in cosmetics for a long time but have they really resulted in active cosmetic products? In order to achieve this, the right active needs to be delivered to the right location at the right concentration for the correct period of time. And the extent (and therefore the concentration) of this delivery depends on the formulation.
From a rather theoretical approach based on the polarity of the active ingredient, the stratum corneum and the oil phase, the Relative Polarity Index was established that enables the selection of a suitable emollient for ensuring skin penetration of the active ingredient. Practical examples subsequently show the validity of this approach that demonstrates that one can regulate the delivery of an active molecule (and therefore the efficacy of a cosmetic formulation) by selection and control of the emollient system.
Cosmetic formulations are generally quite complex mixtures and subsequent experiments using different emulsifier systems indicated that this component of a cosmetic formulation could also have an impact on steering the active ingredient to the right layer of the skin, although it is too early to be able to derive general rules from this.

Keywords

active ingredients, emollient selection, formulation design, octanol/water partition coefficient, skin distribution profiles

Introduction

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 the number of ingredients for which *in-vivo* evidence is also available, is increasing. 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 has indeed its claimed cosmetic activity, questions arise about the formulation development process that assures that the active ingredient is transformed to an active cosmetic product. In many cases, companies have a number of standard formulations into which a new active ingredient is incorporated. Following stability testing, small clinical trials are performed to evaluate the claimed efficacy of the active ingredient. In most cases, no efficacy is seen and after some additional work, the active ingredient is discarded.
Whereas the reasons for standard formulations are very understandable, such an approach does not address the principles that underpin skin delivery. This paper aims to describe the selection criteria for ingredients in cosmetic formulations to optimize the delivery of an 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 paper are, therefore, only guidelines but, although still not fully optimized, will be a lot closer to a final 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

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. It then 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 either into the blood capillaries or fat deposits. From this, it can be concluded that both partition and diffusion are very important determinants for 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. Potts and Guy elegantly demonstrated that the permeability of a chemical through the stratum corneum could be estimated from only two parameters, the octanol/water partition coefficient and the molecular weight [2]. Of the two, the partition coefficient had a bigger influence as evidenced by the weighting factors in the formula they derived:

$$\log k_p\ (cm/s) = -6.3 + 0.71 \log K_{oct/water} - 0.0061 \cdot MW \qquad \text{(Eq. 2)}$$

in which MW is the molecular weight of the penetrating molecule. In short, this formula indicates that when the lipophilicity of a penetrating molecule increases, the permeability increases and when its molecular weight increases, the permeability decreases. The unit, cm/s, indicates that the permeability basically reflects the speed with which a chemical diffuses through the stratum corneum.
In order to get a chemical into the skin, it needs to partition from the formulation into the stratum corneum as indicated by the (stratum corneum/formulation) partition coefficient, the $K_{sc/form}$ of the penetrating molecule. This partition coefficient is defined as:

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

in which $C_{\max}^{penetrant}$ represents the maximum solubility of the penetrating molecule in either the stratum corneum or the formulation Therefore, 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. At the same time, $C_{\max}^{penetrant}$ in the formulation (which more or less equals ΔC) needs to be large in order to increase J as reflected in the well-known formula:

$$J = k_p \cdot \Delta C = \frac{K \cdot D}{L} \cdot \Delta C \qquad \text{(Eq.4)}$$

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.

Theoretical requirements for the various parameters
Based on the above, it should be possible to list whether the various parameters, k_p, K, D and solubilities in stratum corneum, formulation and octanol should be high or low in order to enhance delivery. The results are listed in Table I.

Table I *Effect of parameter extent of skin delivery of cosmetic ingredients*

Parameter	Change	Effect	How?
k_p	Greater	Speeding up diffusion rate	Increasing K, D Reducing MW, L
	Smaller	Slowing down diffusion rate	Reducing K, D Increasing MW, L
D	Greater	Speeding up diffusion	Use skin penetration enhancers
	Smaller	Reducing diffusion	Use skin binding to retard penetration
$K_{oct/water}$	Greater	Increased levels in stratum corneum	Make penetrant more lipophilic
	Smaller	Reduced levels in stratum corneum	Make penetrant more hydrophilic
$K_{sc/formulation}$	Greater	Depending on polarity of formulation	Depending on polarity of formulation
	Smaller	Depending on polarity of formulation	Depending on polarity of formulation

When looking at Table I in relation to the purpose of this paper, it appears that the physicochemical properties of the penetrating molecule, the active ingredient that needs to be formulated are key. Changing the octanol/water partition coefficient, $K_{oct/water}$ (by changing the chemical structure of the molecule) or the diffusivity, D (by increasing skin binding via hydrogen bonding in the skin by the introduction of hydroxyl groups) require a repeat of all efficacy studies or, in the worse case, repetition of registration and safety studies. The only parameter that can be easily changed is the $K_{sc/form}$ as this depends on the formulation. This will not be fully investigated when inserting the active ingredient in a limited range of standard formulations.

The influence of formulation characteristics on skin delivery

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

1. 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.
2. 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, but in a somewhat more polar fashion than butanol with respect to its solubilising ability for penetrants [3]. The experimentally determined log $K_{octanol/water}$ of 1-butanol is 0.88 [4]. For the purpose of this work, the polarity of the stratum corneum as expressed by its octanol/water partition coefficient is set at $10^{0.8}$, *i.e.* 6.3.

The Relative Polarity Index (RPI)

The Relative Polarity Index 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:

1. 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 amongst others by the external relative humidity [5]);
2. the polarity of the penetrating molecule;
3. 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.

Imagine the example of an active ingredient with a log $K_{oct/water}$ equal to that of the stratum corneum (0.8) in a formulation with 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 not initially contain any penetrant, *i.e.*, a dilution effect. Such a situation is very unlikely as in reality almost all active ingredients have polarities that differ from that of the stratum corneum. Two situations need to be discussed separately; in the first case the active ingredient is more polar than the stratum corneum and in the second case the active ingredient is more lipophilic than the stratum corneum.

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 1.

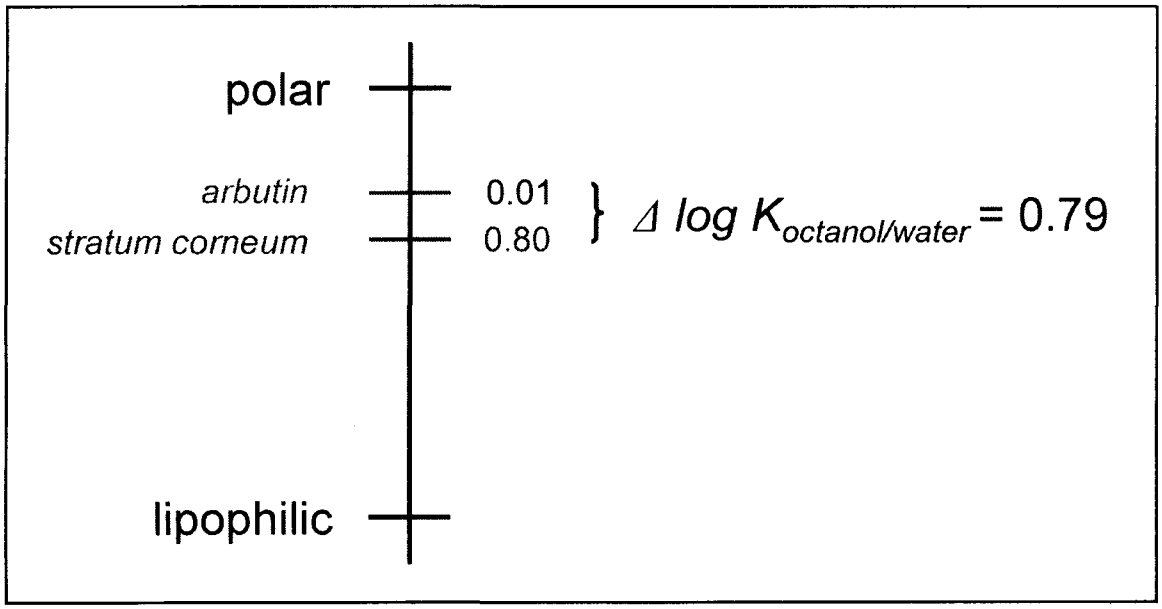

Figure 1 *Visualization of the polarity gap between an active ingredient more polar than the stratum corneum (in this case arbutin) and the stratum corneum using the Relative Polarity Index.*

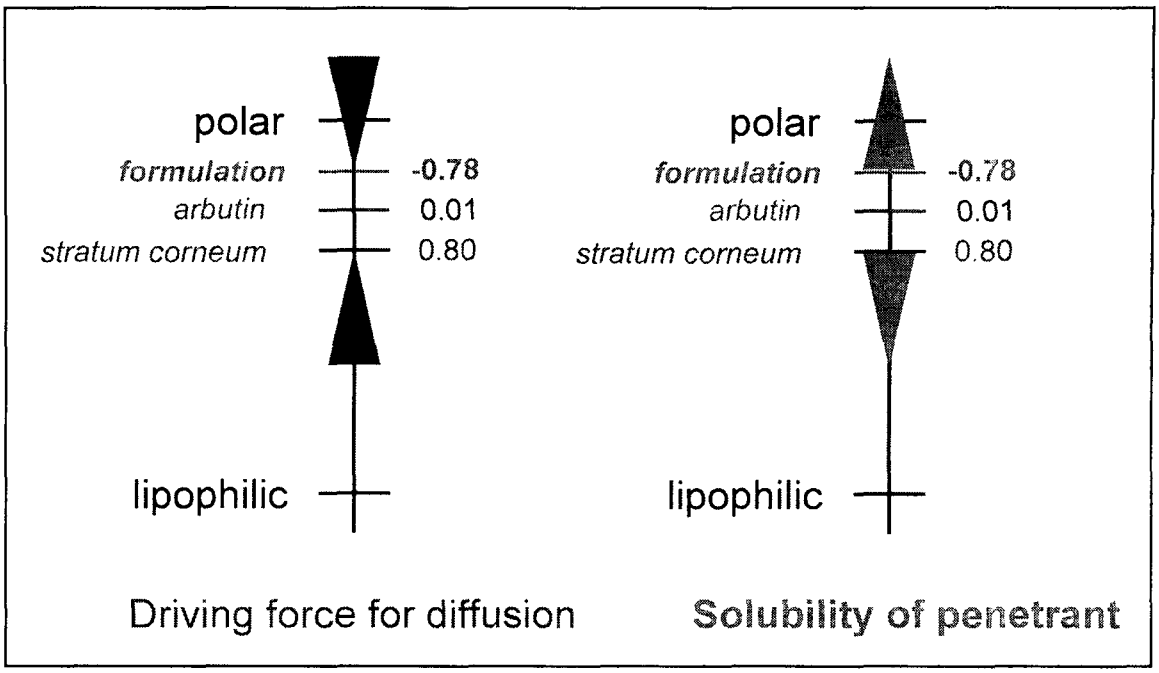

Figure 2 *Example of the calculation of the polarity of a formulation for penetrants more polar than the stratum corneum. Arbutin is used as an example. On the left, the influence of polarity of the formulation on the driving force on diffusion and on the right, the influence of the polarity of the formulation on the solubility of the penetrant.*

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 greater or less than that of the active ingredient itself, *i.e.*., either above 0.8 (0.01 + 0.79) or below –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 2 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 2.
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.

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.

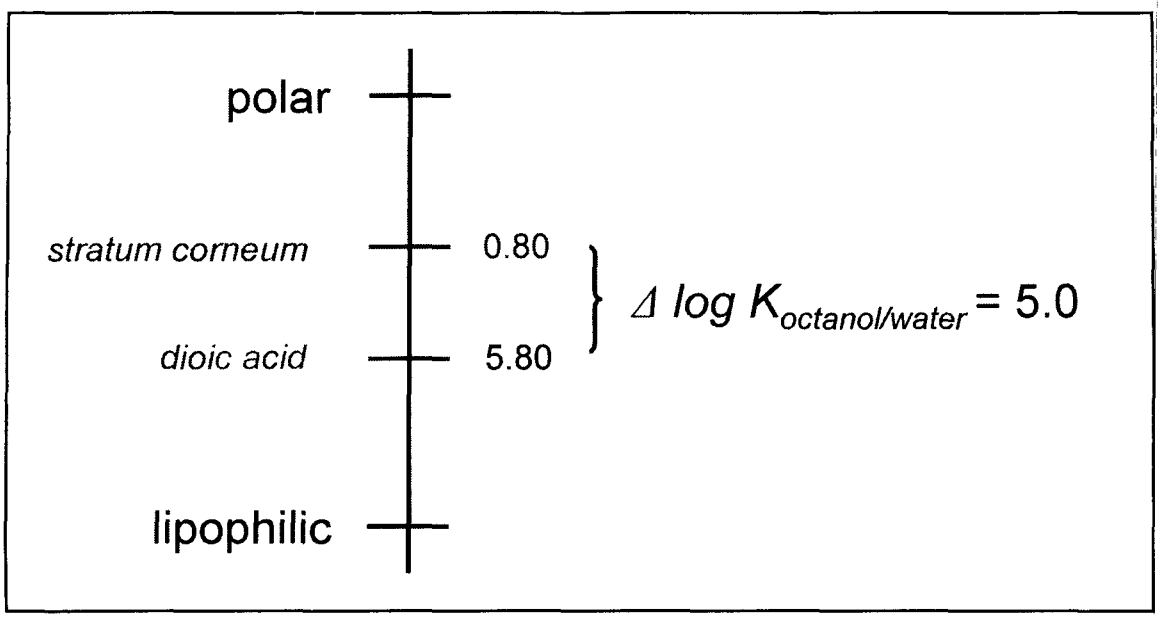

Figure 3 *Visualization of the polarity gap between an active ingredient more lipophilic than the stratum corneum (in this case octadecenedioic acid) and the stratum corneum using the Relative Polarity Index.*

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 3.
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, *i.e.*., 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 corneum than in the formulation and would therefore 'prefer' to be located in the stratum corneum rather than 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 4. 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 4.
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.

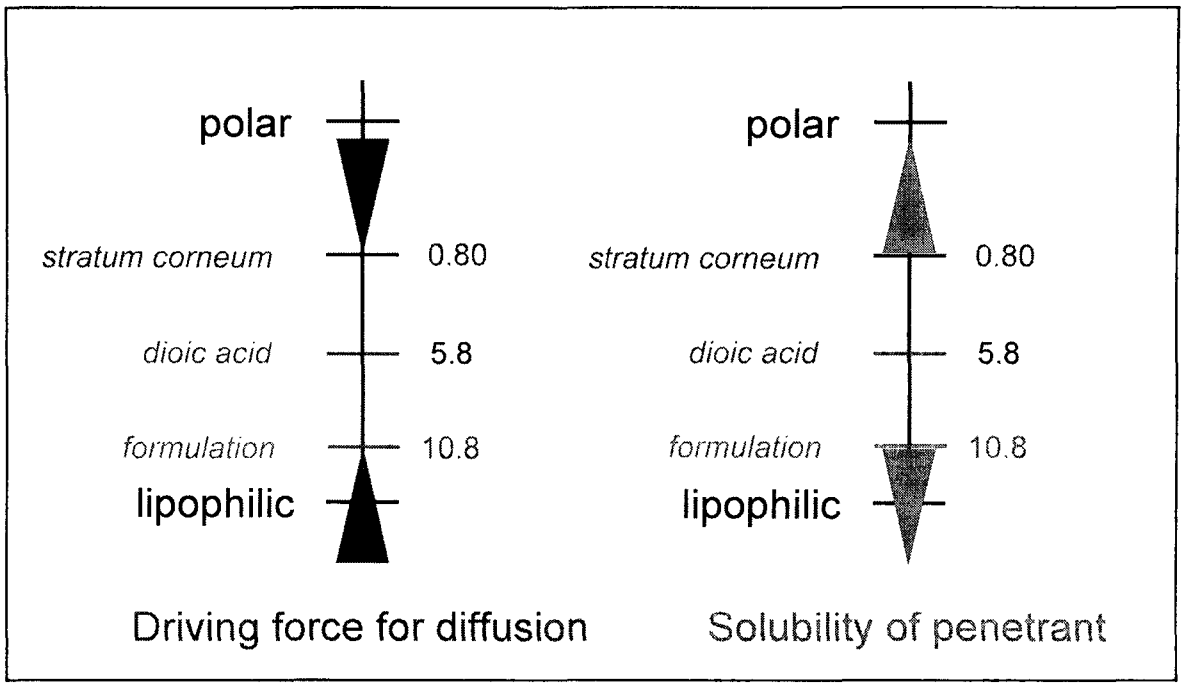

Figure 4 *Example of the calculation of the polarity of a formulation for penetrants more lipophilic than the stratum corneum. Octadecenedioic acid is used as an example. On the left, the influence of polarity of the formulation on the driving force on the diffusion and on the right, the influence of the polarity of the formulation on the solubility of the penetrant.*

Step 1: Optimizing the solubility by selecting the primary emollient or solvent
After having calculated the polarity gap 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 2 and 4? 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, chose an emollient with a polarity 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 II provides RPI values of some typical emollients and hydrophilic solvents that span a wide range and 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.

Table II *Relative Polarity Index values (calculated octanol/water partition coefficients) for some hydrophilic solvents and lipophilic emollients typically used in cosmetic formulations*

INCI name	Calculated log P value
Glycerin	-1.76
Dipropyleneglycol	-1.17 / -1.23
Propylene Glycol	-0.92
Ethanol	-0.32
Triethylhexanoin	2.70
Glyceryl Isostearate	4.76
Isopropyl Myristate	5.41
Propylene Glycol Isostearate	6.08
Isopropyl Isostearate	7.40
Ethylhexyl palmitate	9.12
Ethylhexyl isostearate	10.05
Vegetable Squalane	14.93
Triisostearin	18.60
Trimethylolpropane Triisostearate	20.27
Pentaerythrityl Tetraisostearate	25.34
Isostearyl Isostearate	26.98

An example of using this approach:
An example of this is the formulation of dioic acid for which formulations with a polarity 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 and 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, a formulation was created with the composition as outlined in Table III. Another formulation was made simply based on physical stability of the emulsion system. Its composition is given in Table IV.

Table III *Composition (in w/w%) of a dioic acid-containing o/w-formulation designed according to the Relative Polarity Index principles*

Propylene Glycol Isostearate	15.0
Triethylhexanoin	3.0
Octadecenedioic acid	2.0
Steareth-21	5.0
Steareth-2	1.0
Glycerin	4.0
Xanthan gum	0.2
Phenoxyethanol (and) Methylparaben (and) Propylparaben (and) 2-bromo-2-nitropropane-1,3-diol	0.7
Aqua	ad 100

Table IV *Composition (in w/w%) of a dioic acid-containing formulation designed solely on physicochemical stability*

Caprylic/Capric triglyceride	10.0
Glyceryl stearate SE	3.0
Steareth-21	5.0
Steareth-2	1.0
Cetyl alcohol	2.0
Octadecenedioic acid	2.0
Glycerin	3.0
Benzoic acid	0.2
2-Amino-2-methyl-1-propanol, to pH 5.5	qs
Aqua	ad 100.0

Skin delivery experiments with delivery-optimized and stability-optimized formulations

The formulations described in Tables III and IV were tested separately for skin delivery. For the delivery-optimized formulation, full-thickness pigskin dermatomed to 400µm was used *in-vitro* in a Franz-diffusion cell dosed at a rate of 10µl/cm^2. Cells were left in place for 24 hours after which the formulation was removed, the skin was tape-stripped 21 times and strips, remainder of skin and receptor fluid analyzed to assess skin penetration. For the physical stability-optimized formulation, full-thickness pigskin (500µm) was used *in-vitro* in a Bronaugh flow-through diffusion cell dosed at a rate of 66µl/cm^2. Cells were left in place for 20 hours after which the formulation was removed, the skin was tape-stripped 5 times and strips, remainder of skin and receptor fluid analyzed to assess skin penetration. Results of these experiments are given in Figure 5.

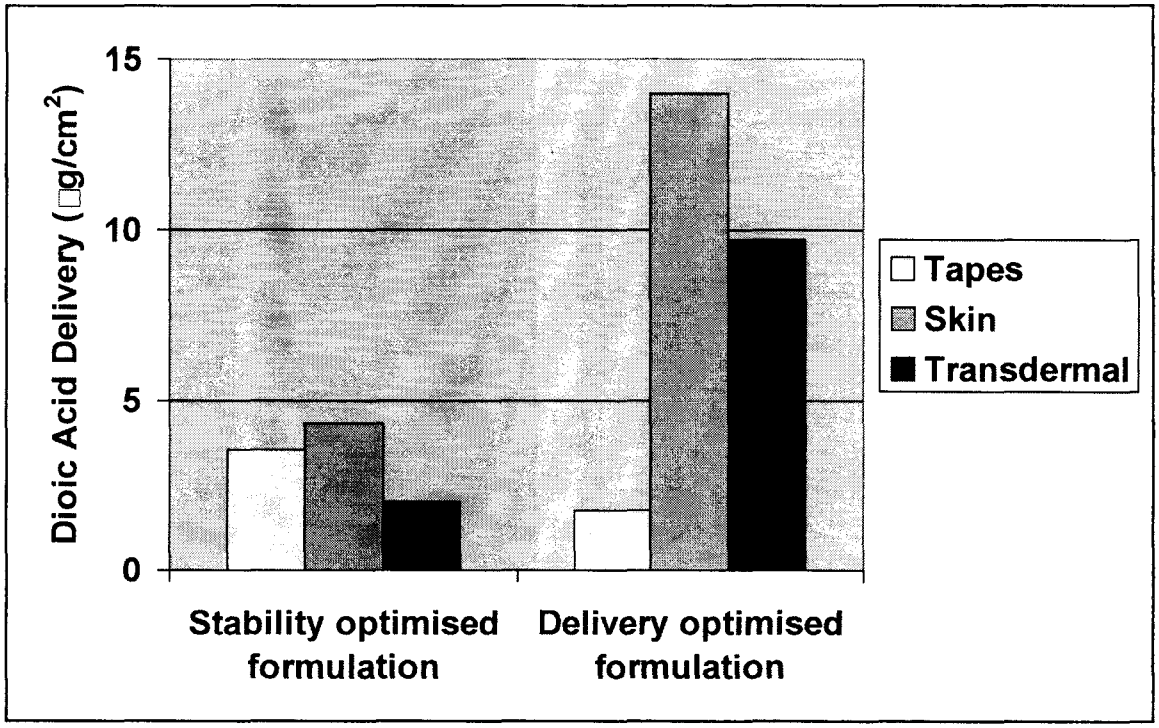

Figure 5 *Skin delivery of octadecenedioic acid of a stability optimized formulation and a delivery optimized formulation according to the Relative Polarity Index principles (for composition, see Tables III and IV, respectively). Note that the latter delivers significantly more dioic acid to the skin.*

As can be seen from Figure 5, the total delivery (*i.e.*, the sum of the amounts recovered in the tapes, the skin and transdermal delivery) is far greater from the delivery-optimized formulation than the physical stability-optimized formulation, 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 stability-optimized formulation (favoring the skin penetration from the stability-optimized formulation), 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 formation of the tyrosinase enzyme [7], the enzyme involved in skin color formation, 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 4.30 to 14.0 $\mu g/cm^2$, without an increase in the concentration of the active ingredient in the formulation. Concentrations of above 2% dioic acid in the stability-optimized formulation were previously tested for skin delivery [8] and demonstrated that a four-fold increase in dioic acid concentration in the formulation (from 2 to 8%) only resulted in a two-fold increase of skin delivery (from 4.3 to 8.0 $\mu g/cm^2$). Based on this and similar experiences, it may 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 emollients greatly influences the total quantity of active ingredient absorbed into the skin. The effect of the emulsifier on skin delivery of active ingredients is also of interest. In order to investigate this, other formulations containing dioic acid were prepared using the RPI concept, *i.e.*, using the same combination of propylene glycol isostearate and triethylhexanoin. The composition of such a formulation can be found in Table V. The only difference from the formulation described in Table III is the emulsifier system. Skin delivery results are depicted in Figure 6 and show that whilst the total amount delivered is high in both cases (due to the choice of emollients 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 in the skin. No explanation can be given for this phenomenon at the present time.

Table V *Composition (in w/w%) of another dioic acid-containing o/w-formulation designed according to the Relative Polarity Index principles using a different emulsifier system*

Propylene Glycol Isostearate	15.0
Triethylhexanoin	3.0
Octadecenedioic acid	2.0
Sorbitan stearate (and) sucrose cocoate	5.5
Glycerin	4.0
Xanthan gum	0.2
Phenoxyethanol (and) Methylparaben (and) Propylparaben (and) 2-bromo-2-nitropropane-1,3-diol	0.7
Aqua	ad 100

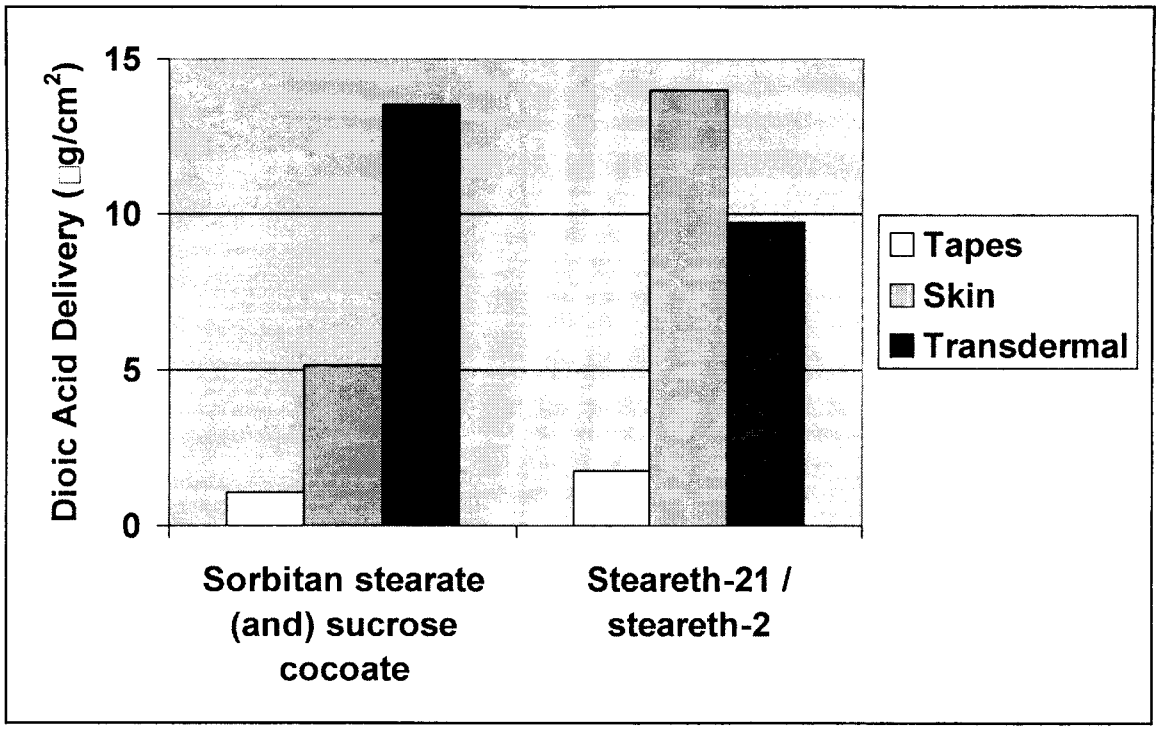

Figure 6 *Skin penetration results of two almost identical formulations, only differing in their emulsifier system. Full composition details of the steareth-2 / steareth-21 formulation are given in Table III and that of the sorbitan stearate (and) sucrose cocoate formulation in Table V. Note that whereas the total amount delivered is high in both cases (and determined by the choice of the emollient(s)), the distribution profile 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 formulations efficacy 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 to 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, as 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.

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