# Clinical Proof for Validity of the »Formulating for Efficacy« Concept: Enhanced Skin Delivery Results in Enhanced Skin Efficacy and Both Can Be Predicted

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## ABSTRACT

*The »Formulating for Efficacy« concept is a systematic approach to simultaneously optimize the driving force of the active ingredient (so that it partitions in larger quantities into the stratum corneum) and reduce its concentration in the formulation without a loss of clinical efficacy. Its ultimate aim is to optimize the clinical efficacy via enhancement of the skin delivery of the active principle at the lowest possible concentration, i.e. at minimal cost. The validity of this approach was initially demonstrated through the use of in vitro skin penetration methodology. A formulation containing 2% octadecenedioic acid that was optimized in this way for skin delivery resulted in 3.5-fold higher concentrations in the viable skin layers than those obtained from a non-delivery optimized formulation containing the same amount of active ingredient.*

*In this paper, clinical studies using the same optimized and non-optimized formulations, as those in the in vitro experiments described above were used to assess whether an enhanced skin delivery also resulted in enhanced clinical efficacy. In addition, a second optimized formulation containing 1% octadecenedioic acid was prepared and compared with the optimized formulation containing 2% of the same active ingredient. All studies consisted of an 8-week application phase. In the two studies with optimized octadecenedioic acid delivery this was followed by a 4-week regression phase. Skin whitening efficacy was assessed using chromametric analysis of skin color.*

*Comparison of the non-optimized and optimized formulations showed that the previously assessed 3.5-fold increase in skin delivery resulted in a 3.2 to 3.9-fold increase in clinical activity of the delivery-optimized formulation. This increase was statistically significant ($p < 0.05$ and $p < 0.002$, respectively), whereas the difference between the two delivery-optimized formulations was statistically insignificant ($p > 0.05$). This confirms the validity of using the "Formulating for Efficacy" guidelines for selecting emollients in topical formulations, as enhanced skin delivery of the incorporated active ingredient corresponds to a similarly enhanced clinical efficacy of the formulation.*

*The enhanced skin delivery from the optimized formulation could be predicted by assessment of the maximum solubility of the active in the non-optimized formulation. It was calculated that the level of active in the non-optimized formulation was only 25% that of maximum solubility and therefore the skin delivery and skin efficacy could be improved by a factor of 4. In addition, the maximization of clinical efficacy could also be predicted by studying the binding curves of the active ingredient to its receptor. Likewise, theory predicts that the skin delivery of two independently optimized formulations containing either 1% or 2% oc-*

*tadecenedioic acid should result in the same delivery of the active ingredient and therefore also the same clinical efficacy. The reality of a clinical study confirmed this theory: the 1% and 2% formulations resulted in equal skin whitening efficacy.*
*It can therefore be concluded that the formulation guidelines of the »Formulating for Efficacy« concept are not only valid in theory or only in in vitro skin delivery set-ups but also in in vivo clinical situations. Moreover, the potential increases in clinical efficacies can be predicted from simple solubility experiments of the active in the formulation.*

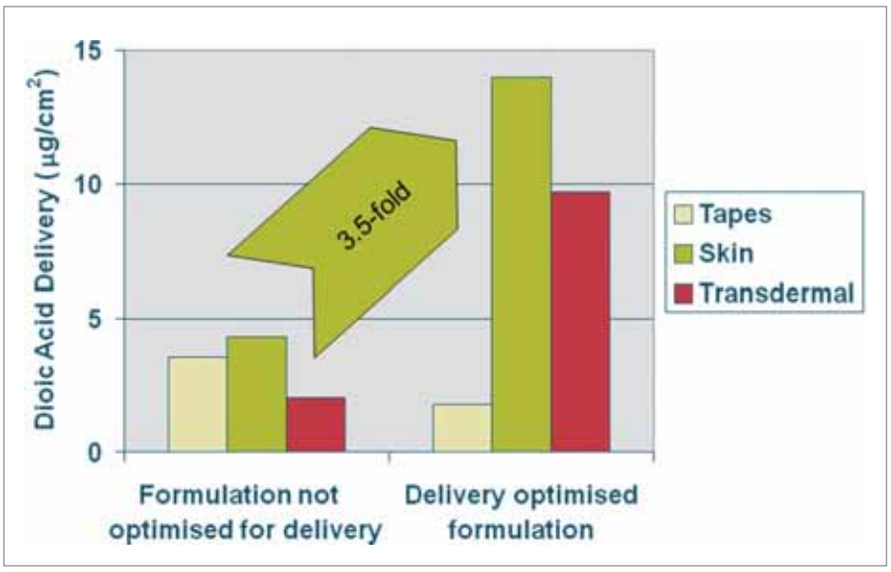


**Figure 1:** Skin delivery of octadecenedioic acid was enhanced by a factor of 3.5 when a non-optimized formulation was optimized for skin delivery. The number 3.5 is, of course, coincidental, as it depends on the choice of the non-optimized formulation. Please note that the 3.5 has been calculated for the skin section, as this is where the melanocytes, the site of action for octadecenedioic acid, can be found. Modified from references [1] and [2].

## INTRODUCTION

Many cosmetic companies in the world want to add special functionalities to their products and therefore intensively search for new biological active ingredients from either a natural or synthetic origin. Identifying an active ingredient with the right intrinsic activity, however, constitutes only half the solution, as the clinical efficacy of a cosmetic formulation is the mathematical product of the intrinsic activity of the active ingredient and its delivery to its site of action. This is illustrated in **Equation 1**. In order to obtain the most efficacious cosmetic product, it is necessary to optimize both factors in this equation: the intrinsic activity of the active ingredient (via the choice of the active) as well as its delivery (via the choice of the formulation in which the active ingredient is incorporated).

***Clinical efficacy = Intrinsic activity • Skin delivery***
**(Equation 1)**

In 2004, two papers were published entitled »Formulating for Efficacy« in which a systematic approach to enhance the skin delivery of active ingredients from topical formulations was outlined [1,2]. In short, two opposing forces need to be optimized to enhance the skin delivery of active ingredients. On the one hand, there should be enough active ingredient in a formulation to allow its minimal effective concentration to be reached at the target site. This is achieved by using a *primary emollient* in which the active ingredient is very soluble such that a *high absolute* solubility is achieved. On the other hand, a formulation containing only this primary emollient would not deliver the active ingredient very well because its driving force for diffusion is far from optimized. The active ingredient simply likes the formulation too much. This driving force to leave the formulation can be achieved by adding a *secondary emollient* in which the active ingredient is not very soluble, and that pushes the active ingredient out of the formulation into the stratum corneum [1,2]. This creates a *low relative solubility* of the active ingredient relative to that in the stratum corneum. In other words, the solubility of the active ingredient in the stratum corneum should be higher than that in the formulation, but the solubility in the formulation should be high enough to allow sufficient active ingredient to be dissolved to be able to achieve clinical efficacy. The exact balance between these two opposing effects depends on the ratio between the primary and secondary emollient. This ratio is determined by the polarity of the active ingredient, the physicochemical properties of the primary and secondary emollients, the ratio of the oil/water phases in the formulation, and finally the concentration of the active ingredient in one of these phases. Previous work demonstrated that when a formulation containing 2% octadecenedioic acid, a skin whitening agent, was optimized according to this »Formulating for Efficacy« concept, a 3.5-fold higher delivery of the active ingredient to the viable layers of the skin where the melanocytes are located was achieved (see **Figure 1**) [1,2]. The enhancement factor of 3.5 was coincidental, as it depended on the quality of the previously prepared formulation (the non-optimized formulation) that was prepared with sensory and

physical stability requirements in mind but was not optimized for skin delivery of the active ingredient. The rational for this new skin delivery-optimized formulation was described previously [1,2]. The composition of these two formulations can be found in **Table 1**. The only difference between the two formulations was the choice of the emollients used.

In the work described here, the clinical efficacy of the two formulations described above is compared. A 3.5-fold increase in skin delivery should in principle also result in a 3.5-fold increase in clinical efficacy. Theoretically, the skin delivery of the active ingredient should only depend on the *relative* concentrations of the active, the primary emollient and the secondary emollient. Therefore, if the oil phase is halved or doubled without affecting the ratios between these three ingredients, the skin delivery (expressed as absolute amount per unit area and time) and therefore the skin efficacy should remain the same. To check this, another study was performed in which the concentration of the active ingredient was halved by removing half the oil-phase in which the octadecenedioic acid was incorporated. Because the driving force for diffusion of an active ingredient is determined by its thermodynamic activity in the formulation (as reflected by its fraction of maximum solubility) and not by its absolute concentration, the active ingredient should be delivered at the same rate from both the 1% and the 2% octadecenedioic acid-containing formulations. Differences will only be found if the absolute quantities present in the formulations are insufficient to achieve the minimal effective concentration at the target site. The composition of the 1% formulation is also given in **Table 1**.

The objective of this paper is threefold. First, it illustrates that changes in formulation composition structure determine the skin delivery of the active ingredient and therefore the clinical efficacy of a formulation (the first comparison between the non-optimized and optimized skin delivery formulation). Second, it demonstrates that it is not the absolute concentration of the active ingredient in the formulation but its fraction of maximum solubility that determines the skin delivery and therefore its skin efficacy (the second comparison between the two optimized skin delivery formulations in which the oil phase was halved, which lowers the absolute concentration but not the fraction of maximum solubility of the active ingredient in that oil phase). Third, this paper demonstrates that these increases in skin delivery and skin efficacy can be predicted from a few simple solubility experiments.

## MATERIALS AND METHODS

The chemical composition of the three formulations that were clinically tested is given in **Table 1**. They were prepared and packed in neutral packaging. In this paper, these formulations are referred to as Formulation A (2% DCA non-FFE-ed, *i.e.*, a formulation that was not optimized for skin delivery containing 2% octadecenedioic acid), Formulation B (2% DCA FFE-ed, *i.e.*, a formulation that was optimized for skin delivery containing 2% octadecenedioic acid) and Formulation C (1% DCA FFE-ed, *i.e.*, a formulation that was optimized for skin delivery containing 1% octadecenedioic acid). DCA stands for octadecenedioic acid and FFE for Formulating for Efficacy, the formulation approach that was used here to optimize the skin delivery of active ingredients.

Three double-blind, double-center studies to investigate the skin whitening capability of skin care formulations were performed. The first study using Formulation A was performed in the United Kingdom on 20 subjects of Indian and Pakistani descent and involved twice daily applications of ap-

**Table 1:** Composition of Non-optimized (A) and Skin-Delivery Optimized Formulations (B and C)

| INCI name | Function | Concentrations (% w/w) | | |
|---|---|---|---|---|
| | | A | B | C |
| Octadecenedioid acid* | Active ingredient | 2.0 | 2.0 | 1.0 |
| Propylene glycol isostearate* | Primary emollient | | 15.0 | 7.5 |
| Triethylhexanoin* | Secondary emollient | | 3.0 | 1.5 |
| Caprylic/capric triglyceride* | Emollient | 10.0 | | |
| Cetyl alcohol** | Emollient | 2.0 | | |
| Glyceryl stearate SE* | Self-emulsifying emollient | 2.0 | | |
| Steareth-21* | Emulsifier | 5.0 | 5.0 | 5.0 |
| Steareth-2* | Co-emulsifier | 1.0 | 1.0 | 1.0 |
| Glycerin* | Moisturizer | 4.0 | 4.0 | 4.0 |
| Xanthan gum*** | Thickener | | 0.2 | 0.2 |
| Preservative | Preservative | 0.2 | 0.7 | 0.7 |
| 2-Amino-2-methyl-1-propanol**** | pH modifier | q.s. | | |
| Water | | ad 100 | ad 100 | ad 100 |

* Croda, Snaith, East Yorkshire, UK; **Cognis, Düsseldorf, Germany; ***Evonik-Goldschmidt, Essen, Germany; ****Mallinckrodt Baker, Inc., Phillipsburg, NJ, USA

**Table 1:** Details from Three Independent Clinical Studies

| Parameter | Formulation A | Formulation B | Formulation C |
|---|---|---|---|
| **Formulation:** | | | |
| Octadecenedioic acid (% w/w) | 2.0 | 2.0 | 1.0 |
| Delivery-optimized | No | Yes | Yes |
| Amount applied (mg/application) | 250 | 350 | 350 |
| **Subjects:** | | | |
| Number of subjects per formulation | 20 | 20 | 20 |
| Subject race | Indian/Pakistani | Chinese | Chinese |
| Test area | Outer arm | Outer arm | Outer arm |
| **Study design:** | | | |
| Time of year | Winter | Winter | Winter |
| Applications per day | 2 | 2 | 2 |
| Duration application phase (weeks) | 8 | 8 | 8 |
| Duration regression phase (weeks) | 0 | 4 | 4 |
| Measuring times (weeks) | 0, 4, 8 | 0, 2, 8 | 0, 2, 4, 8 |
| **Measuring equipment:** | | | |
| Chromameter | CR10 | CR200 | CR200 |

prox. 250 mg of formulation to the outer aspect of the forearm. Chromametric analysis (Chromamater CR 200, Minolta Instruments, Milton Keyes, U.K.) of the skin color was performed at the start (week 0) and at 4 and 8 weeks after the start of the study. A placebo product was applied to the other arm allowing the efficacy of octadecenedioic acid as a skin whitening molecule to be assessed. It was shown that there was a statistically significant skin whitening effect of the formulation containing the 2% octadecenedioic acid ($p = 0.011$) [3]. For the purpose of this paper, however, attention is paid only to the arms that received formulations containing the octadecenedioic acid. Further experimental details can be found in earlier reports describing the active ingredient's clinical efficacy as a skin whitening agent [3] or the study design [4].

The second and third study used Formulations B and C, respectively, and were both performed in China on 20 Chinese individuals of various ethnic groups within China such as Han, Hui, Manchol, Machu, and Ulgur. Twice daily 20 subjects used approx. 350 mg of Formulation B and another 20 subjects used the same amount of Formulation C on the outer aspect of their forearms. In these studies, both formulations were compared with other benchmark formulations that will not be discussed here. A placebo was not included in this study, as the first study described above had already unambiguously proven the clinical efficacy of octadecenedioic acid as a skin whitener. The second and third studies were very similar in their set-up to the first one apart from the fact that the regression of skin color was also studied at weeks 10 and 12 following termination of product application at week 8. This allowed observation of the reversibility of the skin whitening effect. An earlier measuring point at week 2 was also included to allow the potential observation of a faster onset of action. An overview of all relevant study details is provided in **Table 2**.

To allow the results of the three studies to be compared, absolute L*-values corrected for their respective baseline values (*i.e.*, L*-value at time = x minus L*-value at time 0) were plotted and statistically compared using a General Linear Model in SAS (Statistical Analytical Software Institute Corp., Cary, NC, USA). Differences were only considered to be statistically significantly different if p-values were smaller than 0.05.

## RESULTS

Clinically significant skin whitening was obtained in all three studies. Representative pictures of arms at weeks 0 and 8, prior to the start of the application phase and at the end of the application phase, respectively, are shown in **Figure 2**. It can be seen that although a whitening effect was observed for all subjects in all three studies, the visual differences are more pronounced in the photographs originating from Studies 2 and 3 that used the skin delivery-optimized formulations. However, there is no clearly visible difference between the skin whitening effects in Studies 2 and 3 despite their difference in octadecenedioic acid concentration: 2% for Study 2 and 1% for Study 3.

These color differences are more apparent when the change in L*-values is examined relative to baseline, the start of the study averaged over the whole panel, as shown in **Figure 3**. At week 8, relative to Formulation A the $\Delta$L*-values obtained for Formulations B and C were 3.2 and 3.9-fold higher, respectively, whereas the skin delivery of the active ingredient octadecenedioic acid from Formulation B was 3.5-fold higher. The following statistically significant values were obtained:

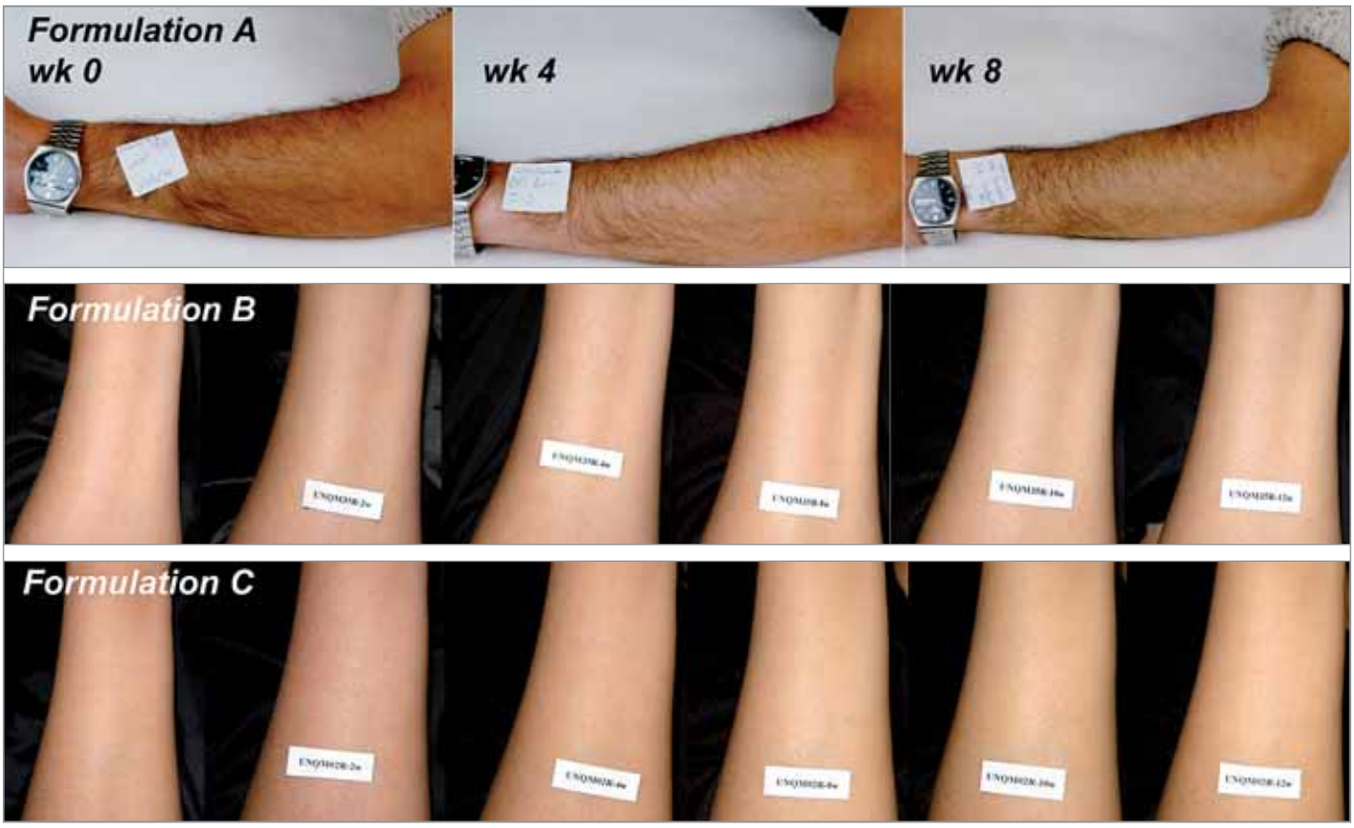


**Figure 2:** Examples of skin whitening following the use of three different formulations, each containing octadecenedioic acid. ***Formulation A*** contained 2% octadecenedioic acid and was tested on Indian/Pakistani skin. The formulation was not skin delivery-optimized according to the »Formulating for Efficacy« principles. Note the skin whitening after 4 and 8 weeks.
***Formulation B*** also contained 2% octadecenedioic but was tested on Chinese skin. A black cloth was used to create an even background for all pictures. This formulation was skin delivery-optimized according to the »Formulating for Efficacy« principles. Please note that the application phase ended at week 8 and that the regression of skin color was minimal in the first 4 weeks after cessation of application.
***Formulation C*** contained only 1% of octadecenedioic acid and was also tested on Chinese skin. The black cloth was also used here. Note that this 1% skin delivery-optimized formulation provided the same degree of skin whitening as the 2% skin delivery-optimized formulation (Formulation B), which is in line with the principles of the »Formulating for Efficacy« concept. Again, the application phase lasted 8 weeks followed by a 4-week regression phase.

(1) ***Formulation B*** vs. ***Formulation A***: $p < 0.05$, demonstrating the influence of optimizing the formulation for skin delivery.
(2) ***Formulation C*** vs. ***Formulation A***: $p < 0.002$, demonstrating the influence of optimizing the formulation for skin delivery and reducing the concentration of the active.
(3) ***Formulation C*** vs. ***Formulation B***: $p > 0.05$, demonstrating that there is no influence of reducing the concentration in a delivery-optimized formulation.

From these levels of significance, it can be concluded that optimizing the skin delivery of a topically applied formulation positively influences the clinical efficacy of the formulation (A/B comparison), but subsequently reducing the concentration of the active in a skin-delivery optimized formulation according to the »Formulating for Efficacy« principles does not necessarily reduce the clinical efficacy of the formulation (B/C comparison).

## DISCUSSION

Previous research indicated that the skin delivery of any active ingredient can be controlled by the choice of the polarity of the phase in which the active ingredient is incorporated. Two aspects are of importance in this respect. On the one hand, there needs to be sufficient active ingredient in the formulation so that the minimal effective concentration can be obtained. This requires the use of an emollient in which the active ingredient is very soluble. Such an emollient is called the primary emollient. In essence, the polarities of the active ingredient and the emollient should match well to very well. Therefore, the primary emollient acts as a good solvent for the active ingredient. However, the use of only this emollient will result in a formulation that has such a high preference for the active ingredient that there is hardly any driving force

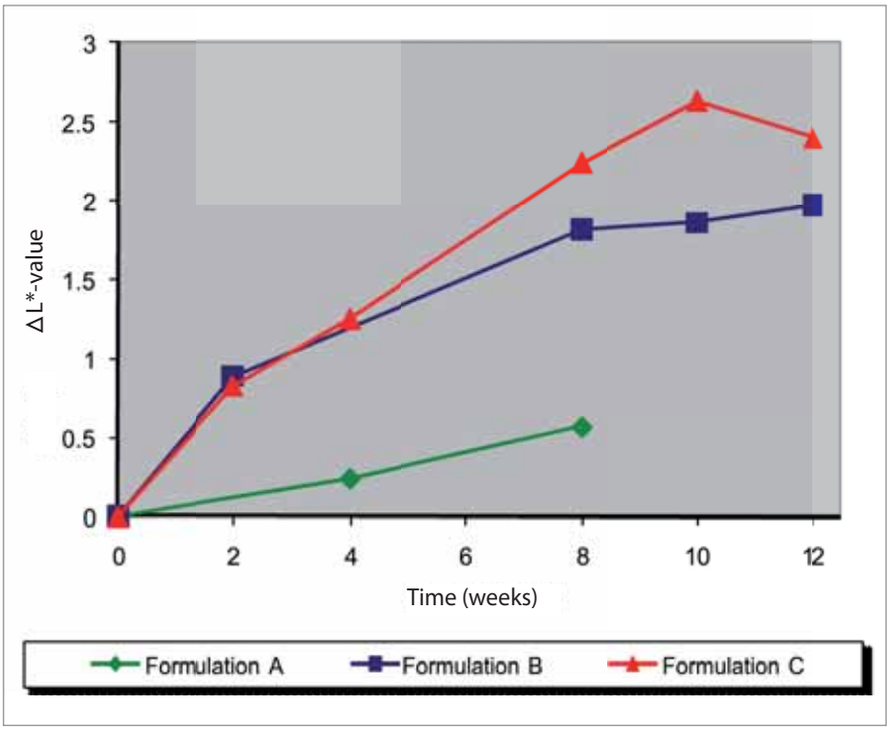


**Figure 3:** Changes in ΔL*-value following application of Formulations A, B and C as measured by the chromameters relative to baseline value at the start of the study. Note that the skin delivery-optimized Formulations B and C demonstrate significantly more skin whitening than Formulation A, which was not optimized for skin delivery ($p < 0.05$ and $p < 0.002$, respectively), whereas the differences between the two skin delivery-optimized formulations are marginal and statistically insignificant ($p > 0.05$).

from the primary emollient to push the active ingredient out of the emollient into the stratum corneum. In other words, the solubility of the active ingredient in the formulation is too high and that in the stratum corneum too small. Whereas it is theoretically and practically possible to change the polarity of the stratum corneum and therefore its capability to solubilize active ingredients, this way of enhancing skin delivery will be ignored in this paper. Another way is to reduce the solubility of the active in the formulation to the extent that the solubility of the active ingredient in the stratum corneum exceeds that of the solubility of the active ingredient in the formulation. Practically, this is achieved by adding to the primary emollient another emollient in which the active ingredient is not very soluble. This creates the driving force for the active ingredient to leave the formulation and go into the skin. Logically, the polarity of the second emollient must be (very) different from that of the active ingredient and the primary emollient. In Formulating for Efficacy terminology, the primary emollient has a low relative polarity index whereas the secondary emollient has a high relative polarity index. The mixture of the two emollients in the right ratio results in a formulation phase with an optimized driving force that still contains enough material to achieve the minimal effective concentration [1,2].

Many suppliers of active ingredients tell their customers that their active needs to be added at a certain concentration to ensure clinical efficacy. An unwritten rule states this level to be 3%, a number for which there is no scientific justification. *Twist* and *Zatz* have beautifully and convincingly demonstrated that every formulation in which an active ingredient is formulated at the same level of thermodynamic activity will deliver this active to the same extent (when skin delivery is expressed as $\mu g \cdot cm^{-2} \cdot h^{-2}$) [5]. The thermodynamic activity of every ingredient in a topical formulation is directly proportional to its fraction of maximum solubility. This means that maximum thermodynamic activity (and therefore maximum skin delivery and maximum skin efficacy) is obtained at the maximum solubility of the active ingredient in the formulation. Twist and Zatz saturated many different solvents with the same skin penetrant and measured their skin penetration. While the absolute concentrations of the saturated penetrant in the formulations varied widely (orders of magnitude), the skin penetration of the penetrant expressed as $\mu g \cdot cm^{-2} \cdot h^{-2}$ of all these formulations was the same [5]. This therefore means that lowering the solubility of an active ingredient in a formulation will increase skin delivery of the active up to the point of maximum solubility. It is therefore scientifically incorrect to state that any active ingredient needs to be included at a given percentage in a formulation to obtain a clinical effect, as this depends entirely on the maximum solubility in the formulation and therefore on the composition of the formulation.

The best way to illustrate this is to study what happens if the concentration of an active is increased in one and the same formulation (*i.e.*, a formulation that is constant in its composition apart from the level of active added to it). This is illustrated by the green line in **Figure 4**. When the concentration in the formulation is increased, skin delivery increases, as does the clinical efficacy, until a plateau is reached. This happens at the point of maximum solubility in the formulation. At this point, the thermodynamic activity of the active ingredient is maximal. However, if the formulation is now changed to contain emollients in which the active ingredient is less soluble, the maximum solubility of the active ingredient in the formulation is reached at much lower concentrations. This situation is

illustrated by the red line in **Figure 4**. »Formulating for Efficacy« is a formulation technique that identifies the right combination of emollients to give the preferred level of solubility of the active ingredient in the formulation. This level can be achieved with many different emollients and »Formulating for Efficacy« therefore does not dictate which emollients *must* be used to achieve this level of solubility. Use of the »Formulating for Efficacy« concept has three possible consequences. First, when an active in a non-optimized formulation (green line) – at a given active ingredient concentration – did not reach the minimal effective concentration at the site of action, it may now reach these concentrations at the target site in the skin at the same concentration of active in the skin delivery-optimized formulation (red line). This is shown in **Figure 4** as Case A. Such formulations now become clinically effective. The use of the »Formulating for Efficacy« concept therefore allows an ingredient claim (where the presence of an active ingredient in a formulation is claimed but not its clinical efficacy in the product) to be changed to the commercially much stronger product claim (where the clinical efficacy of an active ingredient from the cosmetic product is claimed) [6]. Alternatively, already efficacious formulations may become much more effective without adding more active ingredient, allowing enhanced or maximized efficacy of such a formulation to be claimed (Case B). As a third possibility, using the »Formulating for Efficacy« concept allows formulators to use less active ingredient, which is financially attractive, without a loss of clinical efficacy (Case C). These three possible benefits of the »Formulating for Efficacy« concept are all presented schematically in **Figure 4**.

Although the skin delivery benefits of the »Formulating for Efficacy« concept are scientifically very plausible, there previously was no clinical evidence for its validity. In order to prove this concept clinically, three clinical studies were performed in which the active ingredient was not changed (*i.e.*, no change in the intrinsic activity, as mentioned in **Equation 1**) but the skin delivery was changed by modifying the formulation. In this way, the clinical efficacy will be directly proportional to the skin delivery of the active ingredient. Chosen as the active ingredient for these experiments was octadecenedioic acid, which is the dicarboxylic equivalent of oleic acid. This molecule was shown to act as a skin whitener via its binding to the $\gamma$-isoform of the peroxisome proliferator-activated receptor (PPAR$\gamma$), which results in a reduced transcription of the gene that transcribes for tyrosinase, resulting in reduced levels of tyrosinase mRNA, tyrosinase and ultimately melanin [7]. The first clinical study using Formulation A showed a clinically perceivable effect (see **Figure 2A**), but the effects were small. In **Figure 3**, it can be seen that the average difference in L*-values between the start and end of the study ($\Delta$L*) was about 0.57, whereas 0.5 is claimed to be the minimal difference perceptible to the human eye [8]. In other words, the minimal effective concentration was reached but was the whitening effect maximized?

If skin delivery-optimized formulations of octadecenedioic acid resulted in enhanced concentrations of the active ingredient at the site of action, more clinical efficacy should be obtained. Previous work [1,2] revealed that levels of octadecenedioic acid in the overall skin fraction were 3.5-fold higher from a skin-delivery optimized formulation (see **Figure 1**). Because the extent of skin delivery is based on partition coefficients between various

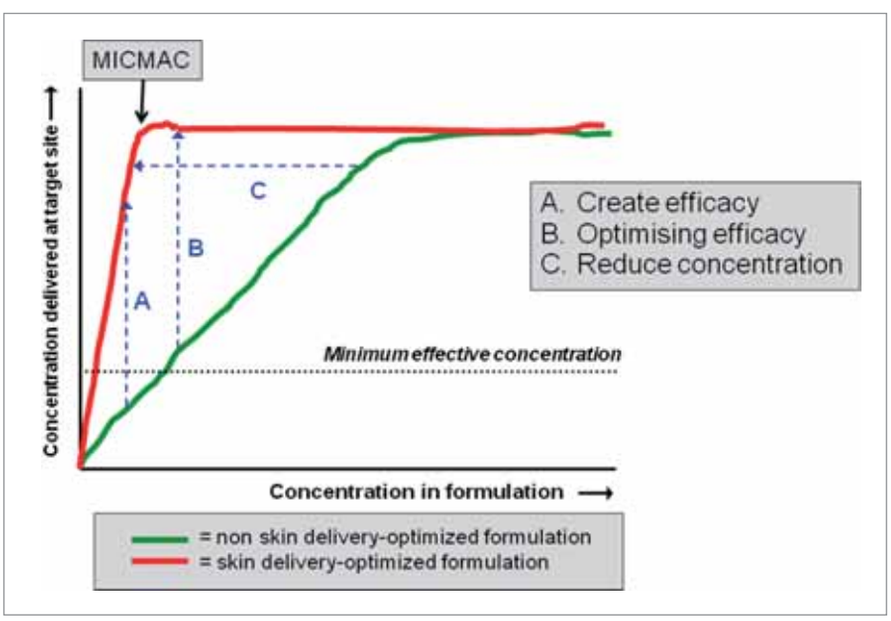


**Figure 4:** Explanations of the various types of benefits of the »Formulating for Efficacy« methodology. The concentration of an active ingredient delivered at the target site as a function of the concentration of this active principle in the formulation is given for a non-skin delivery-optimized (green line) and a skin delivery-optimized formulation (red line). Use of the »Formulating for Efficacy« concept may lead to formulations that at the same concentration of active ingredient are now clinically effective (Case A; creating efficacy) or maximally effective (Case B; optimizing efficacy) or equally effective but at a lower concentration of active ingredient (Case C; cost-reduction by reducing the concentration of the active ingredient in the formulation). Note that the concentration of active ingredient cannot be reduced infinitely, as at one particular concentration (called MICMAC, the minimum concentration of maximum activity) there will no longer be a sufficient quantity of the active ingredient in the formulation to reach the minimum effective concentration (MEC) despite optimal delivery.

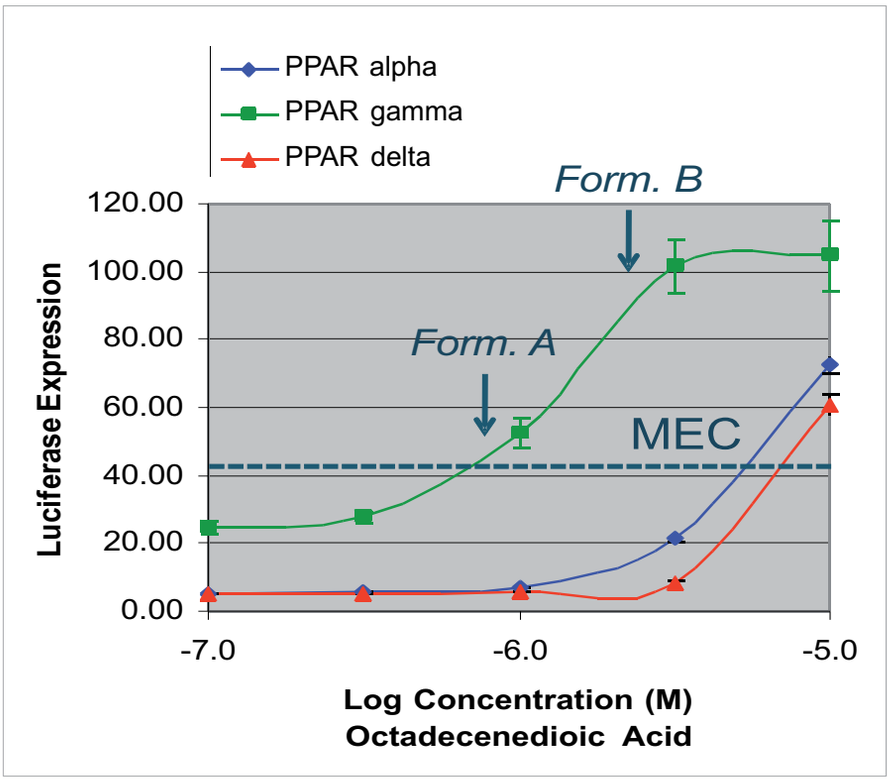


**Figure 5:** Binding curves for binding of octadecenedioic acid to three subtypes of the peroxisome proliferator-activated receptor. As the concentration of octadecenedioic acid increases, luciferase expression increases, which is a direct consequence of the binding of octadecenedioic acid in this reporter gene assay. As the concentration at the target site delivered from Formulation A results in a just perceivable effect (i.e., just above the MEC), one may assume that this value is just below or at 1 µM. It is clear that when the concentration at the target site is increased by a factor 3.5 (when optimizing the skin delivery, as shown in Figure 1), which corresponds to 0.54 on the logarithmic scale in this receptor binding plot, the saturation levels are not reached and therefore there should be a linear correlation between enhanced skin delivery and enhanced clinical effect. At the same time it can be seen, however, that the efficacy is maximum or close to maximum. Modified from Reference [7].

compartments, this automatically implies that the concentration at the site of action is also enhanced by the same factor. However, this does not necessarily mean that the clinical effect will be increased by the same factor, as concentration-efficacy curves may plateau at higher concentrations, for instance when the activity is receptor mediated. The binding curves of octadecenedioic acid to $PPAR_{\gamma}$ [7] suggest that this only starts to happen at significantly higher concentrations (see **Figure 5**). As the clinical effect of Formulation A was just above the minimal effective concentration, the concentration at the target site must have been at the start of the linear increasing part of the binding curve (somewhere around or just below 1 µM). A 3.5-fold increase in concentration at the target site (corresponding to an increase of 0.54 on a logarithmic scale) is still in the linear increasing part of the curve. It can therefore be concluded that this 3.5-fold increase in skin delivery should result in a similar increase in skin whitening activity (see **Figure 5**). At the same time it can be concluded, however, that the effect must have been maximized, as (close to) maximum receptor binding had been achieved at this increased concentration at the receptor site.

The question arises whether the skin delivery enhancement factor of 3.5 could have been predicted. The skin delivery of octadecenedioic acid from the non-optimized formulation was also followed as a function of concentration in the formulation, i.e., only the concentration of octadecenedioic acid changed while the rest of the formulation remained the same. The results of this experiment are shown in **Figure 6** and indicate that the skin penetration of octadecenedioic acid into the skin (dermal delivery) and the systemic circulation (transdermal delivery) increase linearly with the concentration of the active in the formulation [3]. The maximum solubility of octadecenedioic acid in that formulation was also assessed and – within the limitations of the experiment (it is not easy to find small crystals in a white emulsion) – this was determined as 8 ± 0.5%. This therefore means that on purely theoretical grounds, it should be possible to enhance skin delivery by a factor of 8 / 2 = 4 (maximum solubility of the active in the formulation divided by the actual concentration of the active in the formulation). Phrased differently, because the octadecenedioic acid is at only 25% of its maximum solubility in Formulation A, in a skin delivery-optimized formulation (like B) the skin delivery and clinical efficacy can be improved by a factor of 4. Practically, this was also found. The 3.5-fold enhanced increase in skin delivery (**Figure 1**) corresponded to a 3.2-fold increase (Formulation B) or a 3.9-fold increase (Formulation C) in clinical efficacy (**Figure 3**), which averages out at 3.5. Theory and practice are in agreement. The difference between 3.5 and 4 is easily explained by the inaccuracy in the determination of the maximum solubility of the active ingredient in Formulation A.

As mentioned in the introduction, the ratio between primary and secondary emollient is determined among other things by the desired concentration of active ingredient in the formulation. It is the ratio between primary emollient, secondary emollient and active

ingredient that is important and not the absolute concentration of active ingredient. To demonstrate this even more clearly, half the oil phase of Formulation B was replaced by water in Formulation C. As a consequence, the absolute concentration of octadecenedioic acid was halved but the ratios between primary emollient, secondary emollient and active ingredient remained unchanged (when going from Formulations B to C). The thermodynamic activity of the active ingredient that determines the driving force for diffusion remained therefore the same. In other words, not the optimized delivery curve (in red), as shown in **Figure 4**, is changed, but the concentration of active ingredient along the formulation axis (X-axis). The results of the clinical studies indeed showed that there is no loss of clinical efficacy when the concentration of the active ingredient in the formulation is reduced (**Figure 3**).

The prediction that the concentration of the active in the formulation can be lowered without a loss in clinical efficacy was therefore confirmed and provides evidence for the fact that statements like 'this ingredients needs to be formulated at 3% in order to obtain an effect' are not correct. Lowering the concentration from 2% to 1% is illustrated by Case C in **Figure 4**. The only difference from what is shown schematically in **Figure 4** is that in this Figure, the arrow is positioned below the height of maximal clinical effi cacy. Concentrations of octadecenedioic acid can probably be reduced even further without a loss of efficacy, but it should be realized that the absolute quantities of active ingredient incorporated in formulations with ever lower concentrations of octadecenedioic acid will at a certain concentration be insufficient to reach the maximal clinical efficacy. That level represents the most effective concentration for delivering active ingredients into the skin. Theoretical calculations as well as clinical studies are underway to assess this point, called the MICMAC (the *MI*nimum *C*oncentration of *M*aximum *AC*tivity).

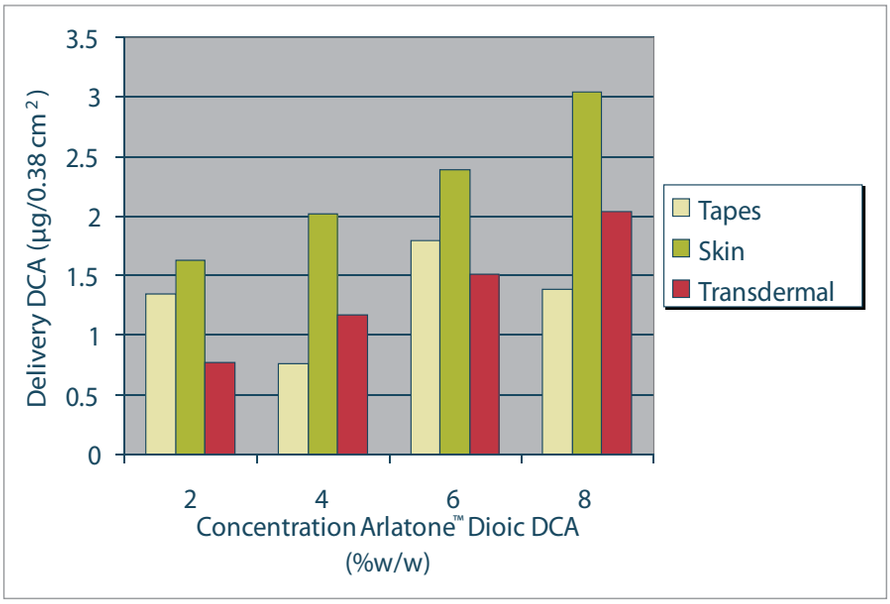


**Figure 5:** *In vitro* dermal and transdermal delivery of octadecenedioic acid (DCA) incorporated at various concentrations in the same base as Formulation A. When the concentration of octadecenedioic acid is 2%, the formulation is in fact Formulation A that was clinically tested in the first study. Note that skin penetration increases linearly with concentration of the active ingredient in the formulation base over the whole concentration range tested. The maximum solubility was assessed to be around 8 ± 0.5%, and therefore the level of octadecenedioic acid in Formulation A was only at 25% of what it could be (2/8 = 0.25 or 25%). The skin delivery of octadecenedioic acid could therefore be enhanced by a factor of 4, which was later confirmed, as shown in Figure 1.

The MICMAC, therefore, is the lowest concentration of an active ingredient in a formulation where maximum clinical efficacy can be obtained.

## IMPLICATIONS FOR THE COSMETIC INDUSTRY

Have we reached the end of formulation optimization from a skin delivery of actives point of view? Fortunately not! Further delivery enhancement can be achieved by using different emulsifier systems that tend to affect the diffusion coefficient, whereas the »Formulating for Efficacy« concept only optimizes the partitioning of active ingredient into the skin. Liquid crystalline structures, for instance, have been shown to enhance the speed of skin penetration of lipophilic ingredients while enhancing the extent of skin delivery of hydrophilic active ingredients [9, 10]. In addition, it is also possible to influence the solubility of active ingredients in the stratum corneum. Recent research has indicated that the skin delivery of water-soluble molecules can also be enhanced by the use of adjuvants like dimethyl isosorbide, diethylene glycol monoethyl ether and pentylene glycol, solvents that all rapidly penetrate the stratum corneum and make it somewhat more hydrophilic, which facilitates the partitioning of water-soluble active ingredients into the stratum corneum [11, 12]. The same principle has also been described in pharmaceutical formulation development where a direct correlation was found between the concentration of propylene glycol in the formulation and the extent of skin delivery enhancement [13].

Therefore, the skin delivery of active ingredients in cosmetic products can, will and needs to be further enhanced not only from a technical but also from a commercial point of view. Optimizing skin delivery is the most effective

way to create more efficacious cosmetic products, especially with the increased regulation of marketing new active ingredients. It is estimated that less than 5% of all marketed cosmetic formulations deliver their active ingredients effectively (i.e., at maximum thermodynamic activity), so there is considerable room for improvement, both in terms of efficacy and cost-reduction of the active ingredient. This can be achieved through the use of the »Formulating for Efficacy« concept but also in combination with other skin delivery enhancing methods. With this new clinical validation of the »Formulating for Efficacy« concept, modifying the skin delivery of active ingredients is no longer a theoretical curiosity but a fundamental tool to improve both the efficacy and costs of topically applied cosmetic and pharmaceutical preparations.

## CONCLUSION

Enhanced skin delivery of active ingredients achieved with the »Formulating for Efficacy« concept was shown to result in a similar enhancement of the clinical efficacy. Formulation B, which delivered 3.5-fold higher amounts of active ingredient into the skin than Formulation A, gave a 3.2-fold higher skin whitening effect in a clinical trial, as determined by the increased change in ΔL* relative to Formulation A.

Reduction of the concentration of the active ingredient while maintaining the ratio between primary emollient, secondary emollient and active ingredient resulted in a significant reduction in active ingredient concentration and therefore costs with no loss of clinical efficacy. This demonstrates that suggested in-use concentrations of active ingredients (as often stated by suppliers) are scientifically invalid, as this level depends on the formulation just as much as the active ingredient. Formulation C showed a similar change in ΔL*, despite its lower concentration of active ingredient.

It is anticipated that the skin delivery of active ingredients in over 95% of topical formulations currently on the market can be enhanced by applying the »Formulating for Efficacy« concept. When combined with reductions in concentrations of active ingredient used, significant cost savings for the cosmetic industry can be achieved. Probably equally interesting, however, is the fact that just a few simple solubility experiments can accurately predict the extent to which skin delivery and skin efficacy can be enhanced.


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### References


[1] *Wiechers, J.W., Kelly, C.L., Blease, T.G.* and *Dederen, J.C.*, Formulating for efficacy, Int. J. Cosmet. Sci., **26** (2004) 172-182; *Wiechers, J.W., Kelly, C.L., Blease, T.G.* and *Dederen, J.C.*, Formulating for efficacy, IFSCC Mag., **7** (2004) 13-20.

[2] *Wiechers, J.W., Kelly, C.L., Blease, T.G.* and *Dederen, J.C.*, Formulating for Efficacy, Cosmet. Toilet., **119** (2004) 49-62.

[3] *Wiechers, J.W., Groenhof, F.J., Wortel, V.A.L., Miller, R.M., Hindle, N.A.* and *Drewitt-Barlow, A.*, Octadecenedioic acid for a more even skin tone, Cosmet. Toilet., **117** (2002) 55-68.

[4] *Wiechers, J.W., Oakley, C.J., Wortel, V.A.L.* and *Barlow, A.*, Looking at the skin: Skin color, Cosmet. Toilet., **113** (1998) 61-69.

[5] *Twist, J.N.* and *Zatz, J.L.*, Influence of solvents on paraben permeation through idealized skin model membranes, J. Soc. Cosmet. Chem., **37** (1986) 429-444.

[6] *Wiechers, J.W.* and *Wortel, V.A.L.*, Creating effective claim support packages, Cosmet. Toilet., **114** (1999) 51-57.

[7] *Wiechers, J.W., Rawlings, A.V., Garcia, C., Chesné, C., Balaguer, P., Nicolas, J.-C., Corré, S.* and *Galibert, M.-D.*, A new mechanism of action for skin whiteners: Binding to the peroxisome proliferator-activated receptor, Int. J. Cosmet. Sci., **27** (2005) 123-132.

[8] Personal communication *Julian Hewitt* 2005.

[9] *Wiechers, J.W., Kelly, C.L., Blease, T.G.* and *Dederen, J.C.*, Formulating for fast efficacy: Influence of liquid crystalline emulsion structure on the skin delivery of active ingredients, IFSCC Mag., **9** (2006) 15-21.

[10] *Otto, A., Wiechers, J.W., Kelly, C.L., Dederen, J.C., Hadgraft, J.* and *Du Plessis, J.*, Effect of emulsifiers and their liquid crystalline structures in emulsions on dermal and transdermal delivery of hydroquinone, salicylic acid and octadecenedioic acid, Skin Physiol. Pharmacol., **23** (2010) 273-282.

[11] *Rossi, P., Wiechers, J.W.,* and *Kelly, C.L.*, Improved delivery and efficacy with dimethyl isosorbide, Cosmet. Toilet., **120** (2005) 107-111.

[12] *Otto, A., Wiechers, J.W., Kelly, C.L., Hadgraft, J.* and *Du Plessis, J.*, Effect of penetration modifiers on the dermal and transdermal delivery of drugs and cosmetic active ingredients, Skin Pharmacol. Physiol., **21** (2008) 326-334.

[13] *Herkenne, C., Naik, A., Kalia, Y.N., Hadgraft, J.* and *Guy, R.H.*, Effect of propylene glycol on ibuprofen absorption into human skin *in vivo*, J. Pharm. Sci., **97** (2008) 185-197.



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