Formulating the Carrier Phase for Clinical Success

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The need

Many skin care formulations feature active ingredients (for the sake of this article, all materials that are intended to have an effect on the skin, whether cosmetic or drug, will be referred to as "actives" or "active ingredients"). The appeal of these products is that there is an expected function, measured or implied, based on the inclusion of an active. Formulators select actives based on an effect, and consumers purchase based on an effect of interest. Very often the desired effect is not realized in the final product with the consumer, though intrinsic effect of the active was promising. What is a formulator to do, to avoid this in the future?

The dilemma

Very often clinical trials are performed on a skin care product containing an active ingredient at the use level suggested by the manufacturer of the active. The measure can be for whatever claim that the marketer is looking to make, whether against a baseline or against a competitive product. At times, probably more often than many marketers would like to admit, the results do not meet expectation. Sometimes there is no effect or difference from control or competition, sometimes the results show some positive direction, but are not eye catching or statistically significantly different enough for a strong claim to be made. At this point in the development and testing process, there is a critical decision to be made.

The decision

When claims work on a product containing and active proves to be inconclusive or fabulously mediocre, there can be a crisis with which to be dealt. The tough decision may have to be made not to launch the product, and reformulate for better results. Another option can be sticking with the product as it is, hoping that the consumer will see the results in spite of what the claims substantiation data would indicate. A third option is to keep the formulation as it is, but reduce the level of active ingredient to miniscule levels, so that it is still on the label, but barely in a quantity greater than the ink used on the label of the package to promote the inclusion of the active. Again, how can being placed in this unenviable situation be avoided?

The expense

Everything around launching a skin care product is expensive, especially if the product is going to contain an active ingredient with a certain performance claim associated with it. Developing the formulation is expensive, often complicated by stability issues brought on by the inclusion of an expensive active ingredient. The clinical claims substantiation work is very expensive, and the advertising and promotion expense to launch a product can be ghastly. The litigation expense, if a product does not meet the claimed performance, can be costly in terms of legal fees, distraction, and negative publicity. Finally, the cost of reformulation and gaining new customers when a product does not succeed is not insignificant.

The appeal

Formulating the carrier phase for clinical success, or Formulating for Efficacy™, can be a valuable pre-formulation activity. Giving the active ingredient the best chance to reach the target of activity, the upper layers of the skin, can allow intrinsic activity to be translated into realized activity. At times, a lower level of active can be used to attain the same effect. More importantly, clinical trials may only have to be performed once for good results, and marketers being able to avoid uncomfortable decisions arising from poor or inconclusive results. Most importantly, the formulation marketed has the best opportunity to see sustained sales as customers see results and tell others of the virtues of the product.

The approach

In order for an active ingredient to have the best chance to diffuse to the skin, it must be in a liquid state. Materials in a liquid state diffuse roughly 10,000 times more readily than solids. Even extremely small solids, down to 10 nanometers, have an extremely difficult time entering the upper layers of the skin. So, the first order of business in formulating for clinical success is to make sure that an active ingredient stays in solution in the formulation and when applied to the skin. Once that is attained, including a material to drive the active from the formulation to the skin can be very useful.

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The law

Fick's First Law, seen below, which is the mass transfer equation, approximates the rate of an active diffusing to the skin, where K is the Partition Coefficient between the active and the skin, D is the Diffusion Coefficient between the active and the skin, and L is the path length, or the thickness of the stratum corneum, and C is the concentration of the active in the carrier phase.

$$J = k_p \times \Delta C = \left(\frac{K \times D}{L}\right) \times \Delta C \approx \left(\frac{K \times D}{L}\right) \times C^{initial\ formulation}$$

What this tells us is that the formulator needs to make sure that the active is comfortably dissolved in the carrier phase. Careful selection of solvents is key to maximizing delivery, because if an active goes to a solid state on the surface of the skin, the chances of diffusion are diminished.

The confusion of diffusion

If one evaluates the K portion of the equation, there is more to the diffusion story to be revealed:

$$K_{skin/formulation} = \frac{C^{active} in\ stratum\ corneum}{c^{active} in\ formulation}$$

Consequently, to maximize K, the carrier phase should be formulated such that the active ingredient is dissolved, but not so much as to have the active too comfortable in the formulation. As such, including a secondary material in the carrier phase to limit solubility can induce a driving force on the active, pushing it from the formulation to the skin.

The means

The critical initial step in formulating the carrier phase for clinical success is understanding the solubility characteristics of the active material that is to be formulated. Solvency predictions can significantly accelerate the process. Also having a greater understanding of the physical/chemical properties of the active in question can enlighten as to the potential challenges that the active will present when looking to deliver it to the skin. Such challenges can include a large molecular volume, a high melting point, or a polarity very different than that of the *stratum corneum*. Using software tools to predict these elements can be a valuable way to accelerate the preformulation process.

The options

For understanding solubility characteristics, there is always the tried-and-true method of performing dissolution studies. These can be very tedious, often inconclusive, and best left to high-throughput robotic operations. Octanol/water partition coefficients (log P) are a favorite of pharmaceutical scientists, but have limited utility for cosmetic active materials. Dielectric constants and Hildebrand solubility parameters offer a step up from log P's, but also suffer from offering only a single-dimensional view of solvents and materials to be dissolved. Hansen Solubility Parameters offer a more comprehensive view of the bonding energies of molecules and allow for more accurate predictions of solvency properties.

The energy

Hansen Solubility Parameters have been used in a number of industries for around 20 years, starting with the coatings industry, for matching solvents with materials to be dissolved. They offer a 3 dimentional view of the bonding energies of molecules. – Dispersion forces, Polar forces, and Hydrogen Bonding forces – and use the numbers assigned to these bonding energies to find suitable mates for such ingredients as actives. The cosmetics and pharmaceutical industries are relative newcomers to the use of Hansen Solubility Parameters. More involved software tools also take into account molecular volumes of solvents and actives to predict solvency characteristics. As well, these parameters are used in such software to give insight as to the delivery characteristics of compositions.

The tools

There are several software tools available, including Formulating for Efficacy™ Software, which can evaluate the Hansen Solubility Parameters of active ingredients and predict solvency characteristics of potential carriers. These carriers can be either oil-phase emollients, water, or polar solvents like ethanol, propylene glycol, or propanediol. From these predictions, the carrier phase can be formulated to ensure proper solvency for the intended level of active in the formulation. From there, secondary materials can be selected which can push the active to the edge of solubility and allow the active to be driven from the formulation to the skin. First step is solvency, second step is driving force – get the active into the carrier phase, then get it out.

The variables

When evaluating how a formulation might be optimized for delivery of a particular active, it is important to look at what can be varied in order to enhance delivery. The initial decision to be made is to whether the active will reside in the aqueous external phase or in the oily internal phase, assuming that the formulation is to be an oil-in-water emulsion. Upon deciding that, based on solubility characteristics of the active ingredient, there must be a determination of how much active and how much of the carrier phase there is to be as a percentage of the total. From there, combinations of carrier solvents can be selected for maximized solvency and driving force. Software tools can be a vital time saver in this exercise.

The result

Since the cosmetic and pharmaceutical industries are relative newcomers to the use of Hansen Solubility Parameters in the science of carrier phase optimization for the enhancement of active delivery, there is limited published *in-vivo* data on the subject. As well, there will be hesitancy of some companies to share the secret of their product success. In unpublished work by Dr. Johann Wiechers, octadecene dioic acid, a waxy, lipophilic skin lightening active, was formulated into a standard emollient carrier phase of caprylic/capric triglyceride and in a carrier phase optimized for solubility and driving force. Franz cell diffusion studies showed a greater than 3-fold increase in delivery in the optimized carrier, and a corresponding 3-fold increase in skin lightening *in-vivo*. Further work demonstrated that the active could be reduced in half and maintain the same clinical effect, assuming that the carrier phase was kept at the optimum ratio.

The rate

Active ingredients will diffuse to the skin at a certain rate based on their molecular volume, physical form at skin surface temperature, and difference in polarity between the active and the *stratum corneum* barrier. Knowing the challenges up front that an active ingredient poses can be of great advantage to the formulator. Also, being able to model how various formulation changes affect diffusion can be very helpful. Modern software tools can not only model delivery of active ingredients over time, but can also track the other materials the carrier phase. The goal is always to leave no active stuck on the surface of the skin.

The skin

The *stratum corneum* is a hydrophobic barrier comprised of an organized structure of water, lipids, wax esters, ceramides, phospholipids, and other materials. The goal for active delivery is to build a system whereby actives can diffuse into the barrier at a reasonable rate. What is to be avoided is compromising the barrier. An aligned strategy to carrier phase optimization based on solvency and driving force is to formulate systems that have a polarity similar to that of the stratum corneum. Often, this can be accomplished alongside the carrier phase optimization with the use of software tools and Hansen Solubility Parameters.

The evaporation

Oil-in-water emulsions are the primary vehicle for skin care products. Immediately upon application, the water is evaporating, often at a rapid rate. This induces phase changes in the emulsion, either causing the emulsion to break, invert, or go to a liquid crystalline state. Especially with regard to actives in an aqueous phase, the formulator must take this evaporation into account. Often it is wise to formulate a secondary, less volatile solvent into the aqueous phase in order to keep the active in solution as the water quickly leaves the premises, usually much faster than a hydrophilic active can diffuse into the hydrophobic *stratum corneum.* In such cases, formulating an oil-in-water liquid crystalline lamellar phase stabilized emulsion which evaporates more slowly, rather than a classic charge-stabilized or steric-stabilized emulsion can be of great advantage.

The limitations

Modern software models are predictive tools and are no substitute for actual work. Software tools can allow the structure of an active or carrier material to be plugged into the model and have the Hansen Solubility Parameters calculated straightaway. These tools struggle with predicting the character of charged species and must be derived using high-throughput experimentation. In addition, there is the thought that active ingredients over a certain molecular volume cannot diffuse to the skin, no matter what efforts are taken. Having said all that, using such tools and concepts to formulate the carrier phase for ultimate clinical success is a far superior method than placing a suggested level of active into a standard base and doing clinical trials as research, hoping for the best.

The benefits

Delivering on promises, real or imagined, is important in any industry. It is especially so in the cosmetics industry, which is, in the estimation of many, a high-tech luxury-goods business. If an active ingredient is on the label of a skin care product, the implication is that something good is going to happen with the use of the product. Increasing the odds of something good happening can, in the end, save money and make for a more sustained business model. Formulating the carrier phase for clinical success is one way to accomplish that goal.

The rest of the job

We have now shown how to build a formulation that is like fast, great handling automobile. Consumers of cosmetic products are not merely looking for speed. The relationship with a cosmetic product starts with the first look and touch. Building a formulation with great performance but unacceptable, unexciting, or inappropriate aesthetics is like placing an ugly car body on the wonderful engine and chassis we have developed, and expecting it to sell well. In our case, the consumer may purchase the product for the desired effect, but may not make it through the container and the time it will take to see the effect, even with our efforts to accelerate the realization of the effects, before moving on to another product. In the second part of the series, we will tackle the job of aesthetic design.

The end

Or, hopefully, the beginning…