Optimizing Skin Delivery

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This article is the first of a 12-part series edited by Joel L. Zatz, Rutgers University, and Joel Sequeira, Schering-Plough, examining delivery of active molecules to the skin.

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There are many opportunities for the development of new technology to control delivery and target actives to specific skin sites. It is hoped that these articles will encourage innocation to effectively deliver the cosmetic actives currently available as well as those of tomorrow.

Joel Zatz and Joel Sequeira

The success of products containing AHAs has inaugurated a new era in skin-care technology. The products themselves are doing well in the marketplace, but that's not the whole story. Through advertising, magazine articles, Internet chat and personal experience, the public has become aware of the importance of a specific group of "active" ingredients that bring about a positive response in the skin. A corollary is the expectation that additional active compounds will be introduced, leading to additional benefits in the properties and appearance of the skin. The performance standard for modern skin products is inching upward, and effective ingredients are leading the way in meeting ever more demanding consumer expectations.[1]

Issues in the Delivery of Actives to the Skin

In addition to choices of targeted skin sites and delivery technologies, pertinent delivery-related questions include: Where is the active distributed? How rapidly is it absorbed and cleared? What percentage of the amount applied to the skin eventually gets in? How does the choice of delivery system influence these results?

Special attention must be given to compounds that are metabolized. If activity resides within the parent compound, but not the metabolite(s), then metabolism represents an elimination process. On the other hand, the reverse may be true, as in the case of tocopherol acetate and retinyl palmitate. For these compounds, metabolism liberates the active molecule and is therefore an important component of the delivery process.

While the active is the star player, it has to be present in the right place within the skin to function optimally (Who said location is everything?), and can cause problems if significant concentrations develop elsewhere. Among the factors affecting the functionality of the active (see sidebar), two concepts are important here. One is delivery, which implies moving the active to the general area within the skin to enable a positive effect. The other is targeting, which means focusing the active where it is most useful. Obviously, these ideas are related. The most efficient use of an active requires attainment of an effective concentration at the target site accompanied by minimal concentrations where the active is either unproductive or potentially harmful.

This article discusses targeting, as well as delivery technologies and test methods. These are the key concepts in optimizing skin delivery, which is one step on the way to truly optimized formulations.

Optimized Delivery

Optimization is usually defined by engineers as achieving the best product at reasonable cost. In today's competitive environment, time has become more important than the immediate cost it represents. Not only does a delay in product introduction mean lost sales, it also creates losses in market share, visibility, inertia, morale, and causes a general backsliding in the marketplace.

A better definition describes optimiza-

Key words

skin care, active ingredients, delivery, testing, product development

Abstract

For best skin-care product performance, formulators should optimize delivery of actives to the skin by identifying and focusing on the target site using appropriate delivery technology.

Um beste Produktleistung im Bereich Skin Care zu erzielen, sollten Formulierer den Transport von Wirkstoffen in die Haut optimieren, durch angemessene Wahl von Zielort, Transport-Technologie und Vergleichstests.

Pour une performance la meilleure possible des produits de soin, les formulateurs se doivent d'optimiser la mise à disposition des actifs par le choix approprié des sites ciblés, la technologie de la pénétration et des tests comparatifs.

Para mejorar el desempeñ de los productos para la piel, los formuladores deben optimizar la vehiculizacíon de activos mediante la eleccíon adecuada del sitio de aplicacíon, la tecnología de vehiculización y las pruebas de comparación

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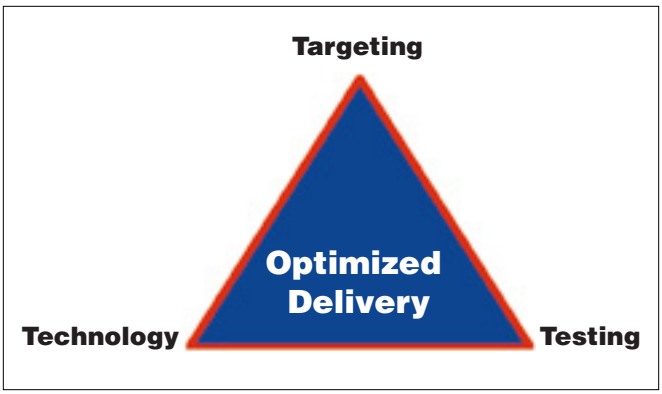

Figure 1. The three T's of delivery optimization

tion as achieving the best product in a reasonable time. Many attributes come into play in defining the "best" skin product. Performance is one of these attributes. Others include stability, appearance, tactile qualities and lack of irritation. Optimizing delivery contributes to product performance while minimizing irritation and other undesired effects.

Let us consider the elements of optimized delivery, outlined schematically in Figure 1. We can think of them as the "3 T's."

The "targeting" vertex of the triangle tells us to embrace the delivery concept and set appropriate delivery goals. Without them, we're shooting in the dark.

The "technology" vertex refers to the means for achieving these goals. We can come up with a wonderful wish list, but it has to be translated into practice, perhaps with a specialized delivery system, perhaps by using familiar formulation ingredients in an imaginative way.

But how do we know how close we are to the mark? This is where the third vertex comes in. Appropriate testing is required to allow a comparison of candidate formulations. Furthermore, the methodology chosen has to allow us to focus on the targeted area. No one single method for evaluating delivery is likely to be applicable to all situations, so it is important to choose a method that makes sense in light of the intended outcome.

Skin Targets

The skin can conveniently be divided into regions where particular products and actives are expected to act. This type of categorization is based on a knowledge of skin properties as well as the mechanism by which various compounds act. Table 1 lists target sites, and examples of compounds or products appropriate for each site.

The skin surface is included as a target, even though it is not formally part of the skin, because it is clearly the place where many products function. For these products, permeation into viable tissues serves no useful purpose, and may lead to irritation or other unwanted side effects (see sidebar: Permeation from the Skin Surface).

The stratum corneum (SC), or horny layer, is the primary skin barrier to penetration, but it is also a potential target for actives. Humectant moisturizers, such as glycerin, apparently bind water within this layer by a simple physical mechanism. (Petrolatum, which also acts as a moisturizer, increases hydration primarily by occlusion.) Most fungal infections of the skin are superficial, and agents used to treat these conditions need penetrate no further than the SC to reach the organisms.

Anti-inflammatory agents, such as corticosteroids, must diffuse through the SC to the aqueous viable tissues underneath to exert their effects. The same is true for local anesthetics, which have to reach the nerve endings.

Antibiotics appear as examples in Table 1 in two places. Some, such as neomycin and bacitracin, are used to prevent infection after cuts and bruises, and products containing such compounds are designed to remain at the surface. Other antibiotics, such as erythromycin and clindamycin used for acne treatment, must diffuse into the follicles to do their job.

Transdermal delivery, as the name implies, represents passage through the skin to reach the capillaries or underlying

Table 1. Skin target sites

Target	Representative function(s)	Examples
Skin surface	Clean; protect; improve skin feel	Soaps, sunscreens, insect repellents, petrolatum, certain antibiotics, emollients
Horny layer	Normalize SC; treat superficial infection	Moisturizers, antifungal agents, keratolytic agents
Living skin cells	Change mitosis rate; block sensory transmission; reduce inflammation	Corticosteroids, local anesthetics, retinoic acid
Sweat ducts	Prevent sweating	Antiperspirant aluminum salts
Pilosebaceous unit	Treat acne and other conditions of follicular origin	Antibiotics, salicylic acid
Capillaries in dermis	Systemic delivery	Transdermal patches (e.g. nitroglycerin, nicotine, estradiol)
Local muscle tissues	Relieve pain	Non-steroidal anti-inflammatory drugs (NSAIDs)

Permeation from the Skin Surface

Products function best at their target site. Soaps and detergents, for example, are intended to cleanse the skin. Excessive permeation into the epidermis may lead to irritation.

In certain instances, permeation is sufficient to affect the performance of protective products. N,N-diethyl-meta-toluamide (DEET) loses its effectiveness over time as an insect repellent because of both evaporation and permeation to underlying tissues and the blood. Neurological toxicity, particularly in children, has been reported following application of high concentrations of DEET.

tissues. Extensive deposition within the skin is undesirable in this instance, as it would delay or reduce the rate of transport to the intended target.

Unfortunately, the skin targets for several important topically applied compounds are not known. This area needs further mechanistic studies of skin function under both normal and impaired conditions, as well as a better understanding of how actives affect the skin.

Delivery Technology

Delivery systems serve a number of useful functions. They help maintain stability of the active, facilitate utilization of the product in a user-friendly manner, and, of course, help direct the active to the target site. Components within the system may alter SC barrier properties, thus promoting increased permeation into the skin. In rare instances, they may actually control the rate of uptake by metering the active's release rate. This is usually possible only for actives with high permeability. Ordinarily, skin transport kinetics are rate-limiting.

Much of the current interest in topical delivery systems was spurred by the introduction of transdermal patches approximately 20 years ago. A patch is an example of a "complete system," in which the entire system is prepackaged and applied to the skin as a unit. The composition is highly controlled, and the flux through the skin usually falls within relatively narrow limits. The total absorption rate is adjusted by varying the area of the device, not the formulation.

At the other extreme are lower-tech, semisolid-type systems similar to traditional ointments and creams. Between these extremes are hybrid systems, in which delivery of the active is manipulated by a special encapsulating module or release-modifying component dispersed in a traditional vehicle. Inclusion of a single novel or well-chosen, conventional ingredient can turn a run-of-the-mill formulation into a product with unique advantages.

Encapsulation of actives by devices such as vesicles, cyclodextrins or microparticulate polymers tends to lower their thermodynamic activity in solution and reduces their tendency to partition into the SC.[2] This can result in a prolongation of residence time at or near the skin surface, and a decrease in the total amount of material penetrating the skin. However, the extent of penetration reduction depends on the fraction of the active that is complexed or otherwise removed from free solution. This distribution is a function of several variables, including the concentration of the encapsulating agent, the number and volume of the fluid phases present, and the affinity of each phase for the active.

Table 2. Skin permeation measurement systems

Human in vivo	blood, urine levels
	disappearance
	bioassay
	skin stripping
	microdialysis
Human in vitro	excised skin
	split skin
Animal in vivo	primates
	mammals
	rodents
	skin flap models
Animal in vitro	furry vs. hairless
Non-biologic	artificial membrane
	calculation; simulation

Test Methods

A variety of techniques, summarized in Table 2, have been employed to

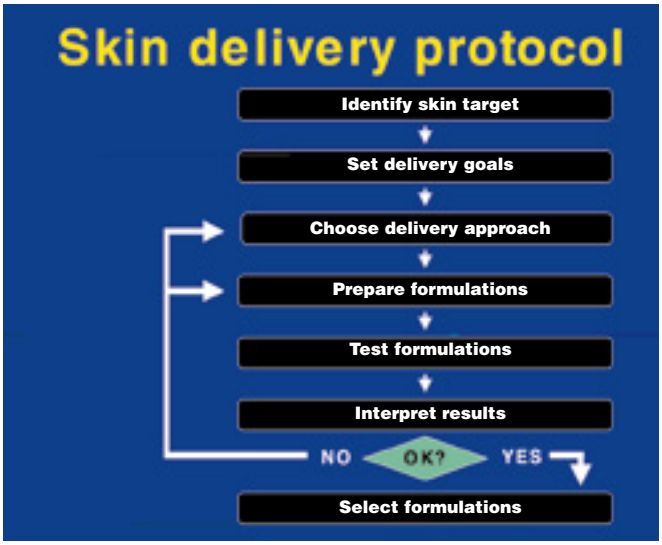

Figure 2. Optimizing delivery during product development

measure skin uptake and delivery.

Human in vivo studies: In vivo methods utilizing human subjects are the most relevant (unless the product is intended for veterinary treatment), but they usually produce the highest variability. Concentrations in blood, urine or other body fluids are very important for evaluating transdermal systems or toxicity screening, However, such measurements do not necessarily relate to skin concentrations and may sometimes be misleading in comparing formulations intended for skin care.

In disappearance experiments, the concentration in the applied solution is measured before and after application to the skin and the amount absorbed is deduced from the difference. [3] The main advantages of this technique are simplicity and the fact that it is noninvasive. However, there is no indication of skin distribution, and analytical errors are troublesome when skin uptake is very slight.

The Blanching Test for Corticosteroids

Corticosteroids cause local vasoconstriction, which results in skin blanching. The concentration of steroid required is inversely related to the compound's potency as an anti-inflammatory agent, and the initial application of the test was to rank steroids according to their effectiveness.

Eventually it was realized that the same procedure could be used to evaluate delivery from different formulations containing the same active compound at the same concentration.

The procedure acceptable to the FDA for approval of generic corticosteroid products is described in the online document, www.fda.gov/cder/guidance/old098fn.pdf.

Bioassay represents a departure from chemical methods, and relies on a relationship between concentration within the skin and a quantifiable, physiologically-based endpoint. The best example of the application of this principle is the blanching test for corticosteroids (see sidebar: The Blanching Test for Corticosteroids). The blanching test is well established, and is recognized by the FDA as a means of checking supposedly similar products against each other. Companies seeking approval for generic products containing corticosteroids may use the blanching test in place of much more expensive and time-consuming clinical trials to show that their product is bioequivalent to the established (reference) product.[4] Another bioassay (used in research on nicotinic acid derivatives) is based on skin reddening due to vasodilation. But, at this time, the vasoconstriction assay for corticosteroids is the only bioassay sanctioned by the FDA.

Skin stripping is a minimally invasive procedure in which successive SC layers are removed with tape. The tape strips can be extracted and analyzed for content of the active. By making a series of applications and performing the stripping procedure at different times, it is possible to obtain kinetic data.

Skin stripping is of obvious importance when the target site for a given compound is within the SC. It allows direct comparison between competing formulations containing such compounds as humectant moisturizers and antifungal agents. It can also provide indirect information about transport to underlying skin layers, since the SC is the skin's primary transport barrier. Rougier et al. have demonstrated a correlation between SC concentration and the total amount absorbed for many compounds.[5] Based largely on this work, the FDA convened a meeting to discuss methods for evaluating bioavailability that might substitute for clinical trials in the generic product approval process. Although there was great interest in the stripping technique, more data is needed to validate its utility when applied to compounds whose target is within the viable tissues.

Microdialysis has been applied to studies of skin permeation, both in vitro and in vivo.[6] A miniscule semipermeable chamber is implanted in the skin below the area of application. A biocompatible receptor fluid is piped through the device via tubing penetrating the skin, originating and ending at remote skin sites. With this technique, concentrations related to dermal levels can be determined as a function of time. This technique is promising, but few data have been published using it thus far.

Human in vitro studies: In vitro measurements using excised human skin have several advantages. They can be performed quickly with minimal expense. Unapproved compounds can be tested and no Institutional Review Board approval is needed. Certain techniques used in vivo, such as stripping, can also be used in vitro. The membrane can be full thickness skin or skin in which some or all of the dermis has been removed ("split skin"). The latter is particularly useful for the study of compounds with poor water solubility. Major justifications supporting the validity of in vitro experiments are

the importance of passive transport pathways in the SC and the resilience (both mechanical and compositional) of excised SC.

In vitro experiments are especially useful for screening a group of formulations and can provide valuable mechanistic information. The technique is widely accepted for evaluation of systemic toxicity risk following application to the skin. Analysis of only the receptor solution can be misleading, because the skin holds most of the absorbed compound in many cases. Furthermore, analysis of the separate skin layers (at least the SC and viable skin) may provide crucial targeting data.

Animal studies: Both in vivo and in vitro animal studies can be used to compare formulations, but the model must be carefully chosen, and caution must be used when the results are extrapolated to human skin. Rodent skin, in particular, is much more permeable than human skin and may react differently to permeation enhancers. Use of artificial membranes or model calculations is sometimes helpful in assessing global permeation potential of a new compound, but is not a substitute for human skin permeation measurement.

Optimizing Skin Delivery in Product Development

Figure 2 illustrates a pathway for optimizing skin delivery during the product development process.

The starting point is an assessment of the target site. Then specific delivery goals are established. Delivery systems based on appropriate technologies are chosen to accomplish these goals. A series of trial formulations are prepared. These formulations, which may represent different delivery technologies or different formulations of a specific delivery technology, are then evaluated simultaneously in various models designed to "weed out" formulations that do not meet the skin delivery goals.

It may be necessary to revisit delivery system selection or perhaps only to select other formulations in line with the same general idea. Several iterations of this process may be necessary before selection of a final formula and a back-up (especially if two formulas look similar in the various screening models).

It is also wise to evaluate these trial formulations through irritation, stability and esthetic appearance screens, simultaneous to the skin delivery screens, so as to select a truly optimized formulation.

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