Cosmetic Delivery: Are We Crossing the Final Barrier Into Dermatology?

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Summary

The boundary between cosmetics and dermatological products is rapidly fading away but regulatory requirements force our products to be in one or the other category. Because the scientific principles are the same for dermatology and cosmetics, scientifically we cannot distinguish the two.

In an old-fashioned technical sense, the last remaining difference used to be the necessity of an ingredient to penetrate the skin, but current cosmetic products also require their active ingredients to penetrate the skin in order to deliver their often — but not always — superficial effect. So, the only true remaining difference between cosmetics and dermatological products is the regulatory one and regulation varies across the world. Sunscreens, for instance, are over-the-counter (OTC) drugs in certain countries like the US, but cosmetics in most countries in Europe.

This paper investigates the scientific and technical arguments there are for having two separate categories now cosmetic ingredients are not only passing the skin but possibly also the final barrier between the two categories.

Riassunto

La linea di confine tra cosmetici e prodotti dermatologici si sta rapidamente affievolendo mentre le normative forzano i prodotti dermocosmetici ad inserirsi nell’una o nell’altra categoria. Dato che il sapere e le nozioni scientifiche si equivalgono sia per la dermatologia che per la cosmetologia, è sempre più difficile trovare una linea distintiva di confine.

Nella vecchia visione tecnica, la differente attività che distingueva un principio attivo cosmetico da un analogo principio attivo farmaceutico era la necessità dei primi di non penetrare attraverso gli strati cutanei in modo che esplicassero soltanto un attività superficiale. Così, l’unica vera differenza rimasta a distinguere i cosmetici dai prodotti dermatologici è rappresentata dalle leggi che ne regolamentano l’uso e che, fra l’altro, variano nelle diverse parti del mondo. Ad esempio, i prodotti solari sono classificati in alcuni stati degli USA come OTC (over the counter), mentre in Europa appar-
tengono alla categoria dei cosmetici.
Questo articolo cerca di riportare gli argomenti tecnico-scientifici che contraddistinguono le due categorie di prodotti anche perché ora i prodotti cosmetici attraversano non soltanto gli stai cutanei ma probabilmente anche la barriera dermo-epidermica.
INTRODUCTION

The scientific and technical capabilities of the human race are increasing exponentially and by the time we are old and at the end of our lives, we will most probably feel bewildered about the latest developments in technology. The last two decades in cosmetics have also seen drastic changes, in particular the advent of active ingredients in the 1990-ies and more recently, the advent of cosmetic delivery systems. But not only science and technology have progressed, the same can be said for cosmetic regulations and we have also seen dramatic changes in the amount of support that cosmetic firms now have to generate in order to substantiate their claims. This increased regulation, and in particular the increased amount of work involved in cosmetic claim substantiation, most probably came about because the cosmetic industry started to claim drug-like activities for their products without really delivering the effect. In the early days, the sky was the limit. But with the advent of the 6th Amendment to the Cosmetic Directive, things changed. The cosmetic industry had to deliver on its promises in order to be allowed to continue to make its cosmetic claims. Some products definitely did, others did not but thanks to increased regulation, cosmetic firms are now paying much more attention to their claims from a technical point of view than a decade ago.

One way to achieve this was to ensure that a product containing an active ingredient with a claimed intrinsic activity was also delivering this activity to the consumer and for that to happen, it had to be delivered to its site of action in the skin. Skin delivery, hitherto a purely pharmaceutical science, is gradually also becoming an integral part of cosmetic science. No longer was the sky the limit to cosmetic claims but the stratum corneum was the limit. Attempts were made to create even a new category, namely that of cosmeceuticals which is a US category for a group of chemicals with an efficacy profile somewhere between drugs and cosmetics. But when it is already difficult to separate drugs and cosmetics from a scientific, technological and regulatory point of view, does the creation of a third category make things easier?

The only aspect where there has been historically a difference between drugs and cosmetics is in the field of skin penetration. Drugs penetrated skin whereas cosmetics did not. In reality, they did penetrate skin but we did not know this and when we knew, we did not notice an effect. Now the active ingredients in our industry have truly become effective and their effects no longer go unnoticed, but this has resulted in a blurring of the boundary between drugs and cosmetics, hence the question “Are we - thanks to increased efficacy of our active ingredients and the advent of cosmetic delivery systems - crossing the final barrier into dermatology?”

FACTORS AFFECTING SKIN PENETRATION OF ALL CHEMICALS, DRUGS AS WELL AS COSMETICS

In essence, there are four main factors influencing skin penetration that will be discussed in order of decreasing importance: the condition of the skin, the physicochemical properties of the penetrating molecule, the formulation in which it is applied to the skin and finally the dosing conditions. Special attention will be given to differences in these four areas between dermatology and cosmetology.

The condition of the skin

The best way to ensure skin penetration is to apply a topical product to a cut in the skin. One can even argue that the use of a needle is the
Cosmetic Delivery: Are We Crossing the Final Barrier into Dermatology?

The fastest form of topical delivery and although this sounds silly, applications using arrays of micro-needles have already been developed. These needles are long enough to pierce the stratum corneum to circumvent the barrier to skin penetration but not long enough to reach the nociceptors, the pain receptors, in the skin. This delivery is therefore into the viable epidermal layers of the skin [1]. But apart from such extraordinary cases where the barrier is effectively circumvented, the main barrier to skin penetration is in the stratum corneum, the very top layer of skin. Cosmetics are typically applied to normal skin with a healthy stratum corneum and therefore normal barrier function. Dermatological products are applied to diseased skin and depending on the disease the state-of-health of the stratum corneum, and therefore its barrier function, may be affected. Atopic dermatitis and psoriasis, for instance, are characterised by an impaired barrier function [2,3] whereas dry and scaly skin disorders are not always accompanied by an impairment of the water permeability barrier [4]. Because most skin penetration research is done on healthy skin, no clear guidelines exist to guide the dermatological formulator on whether skin penetration is enhanced or reduced in a particular skin disease. The only exceptions are those diseases that are known to affect skin lipid synthesis and organisation, like atopic dermatitis [5]. Here, skin penetration is clearly enhanced.

For the current discussion on the difference between dermatological and cosmetic products, there is either no difference in skin barrier function or the skin barrier function is reduced in certain types of diseased skin. If there is a difference at all, then cosmetics will penetrate skin with more difficulty than dermatological products.

The physicochemical characteristics of the penetrant

Assuming that the skin barrier function is intact, the most important factor subsequently determining skin penetration is the physicochemical nature of the penetrating molecule. Most of skin penetration research in the 1960-ies till 1980-ies concentrated on identifying the optimal characteristics but it is not the purpose of this short paper to review all this. I will therefore simply list which characteristics are beneficial for the penetration of chemicals into skin.

But before doing that, it needs to be explained what is meant by the terms skin penetration, partitioning, diffusion and delivery. Skin penetration is the overall process of a series of subsequent partitioning and diffusion steps. In essence, it is the cumulative amount that disappears from the topically applied formulation into the skin and is the sum of skin delivery (the amount that is found in the skin at a given moment in time) and transdermal delivery (the amount that penetrates all the way through the skin into the systemic circulation). Partitioning is the transport of a chemical (also known as the penetrant and typically a drug or cosmetic active ingredient but it could also be an excipient or an emollient) from one layer into the next, e.g., from a topical formulation into the stratum corneum. This partitioning step is then followed by skin diffusion which is the process of transporting the same chemical within a single layer (in this case the stratum corneum) from its entry site (the formulation-stratum corneum interface) to the site where it exits (the stratum corneum-viable epidermis interface). There, it partitions into the next layer, known as the viable epidermis, diffuses till it reaches the other end at the epidermal-dermal junction, etc. In short, partitioning affects the amounts distributed over two layers, whereas the diffusion affects the speed of trans-
port within a single layer. Each of these consecutive partition and diffusion steps can be rate-limiting step in the overall skin penetration process.

The flux, \( J \), of a chemical through the stratum corneum is described by Fick’s first law of diffusion:

\[
J = k_p \cdot \Delta C = \frac{K \cdot D}{L} \cdot \Delta C
\]

in which \( k_p \) is the permeability coefficient, \( \Delta C \) the concentration difference in drug or active ingredient between formulation and stratum corneum, \( K \) the formulation-stratum corneum partition coefficient, \( D \) the diffusion coefficient within the stratum corneum and \( L \) the length of pathway of diffusion. The permeability coefficient of many penetrating chemicals has been modelled by Potts and Guy [6] and confirms the polarity of the penetrating molecule to be the determining physicochemical factor for skin penetration with molecular weight having a somewhat less important influence. Ideal penetrating molecules:

(i) have an octanol/water partition coefficient, \( P \), of 10-100 (i.e., a \( \log P \) of 1-2);
(ii) have a small molecular weight (ideally below 500 Dalton);
(iii) are uncharged but do have a high dipole moment;
(iv) have a melting point at or below the skin temperature; and
(v) do not have free electron groups (especially oxygen in keto- or hydroxyl-groups) that may cause skin binding to proteins.

Most chemicals do not meet all these requirements but those that do, like dimethyl sulphoxide, penetrate the skin within minutes, if not seconds. Of all the various factors, the polarity, expressed in its octanol/water partition coefficient, is the most important factor in determining skin penetration, followed by the size of the molecule, expressed either as molecular weight or – more correctly – molecular volume [7].

In the context of the current paper, there is absolutely no difference between drugs or cosmetic active ingredients; they either penetrate or they do not penetrate the skin as determined by their chemistry. As the skin is supposed to keep the outside world external, there are not that many molecules that easily penetrate the skin. The downside of the stratum corneum as an effective barrier to skin penetration is that no more than an estimated 5% of all chemicals has the potential to penetrate the skin in meaningful amounts to exert a noticeable effect.

The formulation in which the drug or active ingredient is applied

Assuming the skin is intact and the therapeutic drug or cosmetic active ingredient has the right physicochemical characteristics to penetrate the skin, the next determining factor in whether or not skin penetration will happen is the formulation in which the penetrant is applied on the skin. Two types of influences can be distinguished here. A first is the formulation type (o/w-emulsion, w/o-emulsion, micro-emulsion, gel, etc.) in which the active ingredient is incorporated. This is demonstrated in Figure 1 where the skin penetration of a hydrophilic model drug (5-fluorouracil) was studied from a range of different formulation types. This work is described in detail elsewhere [8] and yielded some interesting observations.
The first was that transdermal delivery is much better understood than dermal delivery. The highest levels of transdermal delivery were obtained from the micro-emulsions, probably because they contained a higher level of surfactant, necessary to prepare the smaller droplets. Transdermal delivery from o/w and w/o-emulsions was often similar in magnitude whereas for dermal delivery, more delivery is observed when the active ingredient or the drug is located in the internal phase of the formulation. This seemingly makes no sense as one would anticipate the delivery from the external phase of an emulsion to outperform that from internal phase, although it should be kept in mind that the 5-fluorouracil concentration in the water phase of the w/o-emulsion was slightly higher than that in the water phase of the o/w-emulsion due to different phase ratios (75% vs 86%). One other interesting observation from this work was that dermal and transdermal delivery were not inversely correlated, i.e., if the transdermal delivery was low, its dermal delivery was not necessarily high or vice versa. One thing became very apparent after having done all the different formulation studies: it is not the concentration that determines skin penetration but the thermodynamic activity of the penetrant in the formulation and it is very difficult to change one aspect of skin formulation without affecting other important factors, in particular the thermodynamic activity. This thermodynamic activity is what can be regulated via the choice of the ingredients of the formulation. In order to create an effective product, two opposing effects need to be optimised. On the one hand, there needs to be enough active ingredient or drug in the formulation to be able to reach the minimal effective concentration, which is achieved via the use of a primary emollient that dissolves sufficient penetrant, whereas on the other hand, there needs to be a sufficient incentive for the penetrant to prefer the stratum corneum over the formulation, which is achieved via the use of a secondary emollient that creates a driving force for diffusion [9].
Figure 2 details how the optimal polarity of the phase in which the penetrant is located can be calculated. Whereas the pharmaceutical industry understands the concept of driving force via optimisation of the thermodynamic activity very well but has problems in dissolving its drugs, the cosmetic industry still thinks in terms of concentrations without acknowledging the existence of a thermodynamic activity. This is an area where an awareness of each others way of working will by default lead to product improvement in both markets.

The dosing conditions

Least important but still exerting an influence are the dosing conditions under which the application takes place. This involves factors like occlusion, which is known to enhance the skin penetration of corticosteroids [10], the frequency of application or the skin temperature. Cosmetic products are typically not applied under occlusion whereas this is sometimes deliberately done in dermatology. Dosing frequency and skin temperature play only really minor roles. The frequency, although prominently stated on cosmetic and dermatological products alike, depends in reality more on the residence time of the formulation on the skin than on the need to replace penetrant that has penetrated the skin. Likewise, cosmetic products are normally applied to skin with a normal skin temperature whereas this may be elevated in diseased skin. However, the skin temperature needs to be increased by 10 °C before getting a doubling in skin penetration. Again, we see that on average the penetration from dermatological products may be slightly higher than from cosmetics.

Overall summarizing, the above suggests that skin penetration from dermatological products will be higher than from cosmetic products, not because of the chemicals but because of the pos-
Cosmetic Delivery: Are We Crossing the Final Barrier Into Dermatology?

Factors affecting clinical efficacy of dermatological products and cosmetics

Clinical efficacy can be defined as the product of intrinsic activity of a drug or active ingredient and its delivery to the site of action in the skin, according to the formula:

\[ \text{Clinical efficacy} = \text{Intrinsic activity} \times \text{Delivery} \]

Delivery is the process of ensuring that the right chemical reaches the right site (the site of action) at the right concentration for the correct period of time. Together, these are called the 4 R's of delivery. But as identified in the previous section, there is no real difference between drugs and active ingredients with respect to its skin delivery, so the difference between the two categories must be due to the intrinsic activity, and even that is not the same throughout the world. Sunscreens, for instance, are over-the-counter (OTC) drugs in certain countries like the US, but cosmetics in most countries in Europe. However, their intrinsic activity will be the same all over the world.

Are we crossing the final barrier into dermatology?

The title of this short review article is the question whether we are passing the final barrier into dermatology and with the information provided above, we should now be able to answer this question.

Molecules need to have an intrinsic activity in order to be able to exert a clinical efficacy and they need to penetrate. In the above discussion, it became clear that molecules do not penetrate because they are a drug or a cosmetic, but because of their physicochemical characteristics. So, the distinction between drugs or cosmetics must come from their intrinsic activity. Certain intrinsic activities are clearly dermatological (i.e., anti-inflammatory), whereas others are clearly cosmetic (e.g., moisturisers). Sometimes, the distinction is not clear as in the case of sunscreens.

The current practice of basing the decision to classify a chemical as a drug or a cosmetic ingredient on its mechanism of action is highly unsatisfactory. Antiperspirants are drugs because they work via a physiological intervention, namely via the contraction of the eccrine glands. The fact that this effect is completely harmless does not seem to have any influence on the decision on how to classify such chemicals. Deodorants reduce the characteristic smell of armpits by killing the micro-organisms that convert non-odorous long-chain fatty acids into odorous short-chain fatty acids. On a superficial level, this seems to be more dangerous, but because deodorants deal with micro-organisms instead of the human being, this is a cosmetic ingredient. It gets even more difficult to explain that under current regulation, it is allowed to include, for instance, skin whiteners in a cosmetic formulation that are drugs in most countries based on their mechanism of action (they clearly affect the normal physiology of the skin), but can be classified as active ingredients if their activity is not claimed. Of course, these whiteners behave irrespective of the claim being made on the label of the container or the leaflet of the advertisement. Unless, of course, you claim that skin whiteners can jump out of the container, read and interpret the claim and act accordingly!

But some clear distinctions between dermatological and cosmetic products can be made. The variability in skin condition may influence the skin delivery of dermatological products. There is a need to optimise the skin delivery of topi-
cally applied drugs, but issues as skin feel are, as a rule, simply ignored although the interest is increasing. In the cosmetic industry, product developers have a wider choice of ingredients than their pharmaceutical counterparts, but cosmetic marketers want their products to have more than only an excellent feel, they also want to make the most far-stretching efficacy claims.

CONCLUDING REMARKS

Are we finally crossing the final barrier into dermatology? This question can be answered in three different ways: scientifically, regulatory and technically. Scientifically, there are no differences between drugs and active ingredients; we have already long passed that barrier. In regulatory terms, we are not passing that final border but we are obliged to obey the law, irrespective of the correctness of the decision criteria of drugs and cosmetics. But technologically, we keep on pushing to identify new delivery systems that allow penetration of ever bigger molecules such as hyaluronic acid or insulin. When that has happened, regulatory authorities may finally decide on a new definition of what is a drug and what is a cosmetic. After all, we are still stuck with a definition that was made when the double helix structure of DNA was not even known. Of course, that definition is out-dated. But until that time, we are simply stuck with an artificial barrier between drugs and cosmetics. And that barrier may turn out to be even more difficult to cross than any other physiological barrier like the stratum corneum. It can only be hoped that regulation will catch up with the developments in the scientific and technological arena and that the gap does not continue to widen, as otherwise one day, the gap will have become too wide and deep to even see the other side.
Cosmetic Delivery: Are We Crossing the Final Barrier Into Dermatology?

References


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