

# The Importance of Penetration Enhancers choice in Topical Products

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Topical products are widely used in the treatment of pain or inflammatory and degenerative conditions. Their undeniable advantage is sufficiently proven clinical efficacy and also a generally favourable safety profile due to their minimal systemic exposure compared to orally used products. It was also demonstrated that exact formulation used is critical for topical analgesic in management of pain conditions. This brief overview emphasizes the important role of different excipients like penetration enhancers which chemical properties suggesting a different disrupting effect on the skin barrier. It summarizes the well-known properties of the skin as a key barrier to any pharmacological effects and focuses on a differences in using different excipients like penetration enhancers.

**Key words:** penetration enhancer, oleyl alcohol, oleic acid, skin barrier.

## Důležitost volby enhancerů penetrace v topických léčivých přípravcích

Topické přípravky jsou široce používány v léčbě bolesti nebo zánětlivých a degenerativních stavů. Jejich nespornou výhodou je dostatečně prokázaná klinická účinnost a také obecně příznivý bezpečnostní profil vzhledem k jejich minimální systémové expozici ve srovnání s perorálně užívanými přípravky. Bylo také prokázáno, že při zvládání bolestivých stavů je u topických analgetik kritické i použití konkrétní formulace. Tento stručný přehled zdůrazňuje důležitou roli různých pomocných látek, jako jsou enhancery penetrace, jejichž chemické vlastnosti naznačují odlišný účinek na narušení struktury kožní bariéry. Shrnuje dobře známé vlastnosti kůže jako klíčové bariéry pro jakékoli farmakologické účinky a zaměřuje se na rozdíly v používání různých pomocných látek jako enhancery penetrace.

**Klíčová slova:** enhancer penetrace, oleylalkohol, kyselina olejová, kožní bariéra.

## Introduction

The idea of administering the medicinal product through the skin, directly to the site of intended effect, is thousands of years old. Various reports of efforts to influence human health with such approaches can be found in the oldest civilizations. Anyhow, the idea of such a method of application is still relevant, and even more, is still gaining in popularity, especially in the treatment of painful and/or inflammatory conditions.

It is very important to think about attributes required for topical products like delivery of active substance in amounts sufficient for clinical efficacy, as small as possible perturbation of the skin barrier properties, reversibility

of their impact on the structure of stratum corneum etc.

For topical application, non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used. A fundamental requirement for their successful therapeutic use is the attainment of their site of action (in quantities sufficient for clinical efficacy without any significant long-term perturbation of the skin barrier properties), which is not determined primarily by the pharmacologically active substance, but by the chosen pharmaceutical form (mostly gel formulations) and the excipients contained (14).

The main advantages of topically applied NSAIDs can be summarized in the following points:

- application directly to the affected site with minimal systemic exposure;
- absence of first-pass metabolism;
- limitation of systemic side effects and drug interactions;
- possibility of administration in patients with impossibility/unsuitability of oral or otherwise systemically administered NSAIDs;
- presumption of good compliance.

## Skin structure

A problem that should be kept in mind when applying medicinal products to the skin, assuming their action in deeper structures or even systemically, is the structure and

overall physiology of the skin. By its very nature, it represents a reliable protection of our body, preventing unwanted contact with potentially harmful substances. While the deeper dermis is composed of fibroblasts, extracellular matrix and rich vascular and nerve plexuses, from the point of view of the barrier properties of the skin the externally located epidermis is crucial. It is composed of keratinocytes arranged in stratum basale, spinosum, granulosum, lucidum and corneum. In the stratum basale, the cells are connected to each other by desmosomes (syn. maculae adherentes), the connection to the basal membrane is through hemidesmosomes. Approximately 5% of the cells present are melanocytes capable of producing the pigment melanin. Virtually all layers of the epidermis contain dendritic cells (Langerhans cells) characterized by their ability to present antigens to lymphocytes or Merkel cells located in the stratum basale and external epithelial sheath of hair follicles. Each of these layers has its own specifics.

From the point of view of barrier function, we need to mention the important compactness of the basal lamina at the interface of the stratum basale and the deeper dermis. Let us also mention the importance of the extracellular matrix, especially in the stratum granulosum, whose cells release lamellar granules formed by a lipid bilayer into their surroundings. The contained material has a similar function as the intercellular sealant and the barrier preventing the penetration of foreign substances. The above-mentioned well-developed desmosomes are detected up to the level of stratum lucidum. Last but not least, the process of keratinization is important, as a result of which superficial cells consist only of fibrillar and amorphous proteins, i.e. without cytoplasmic organelles, stored in a lipid matrix composed of ceramides, cholesterol and fatty acids. Their cytoplasm is rich in keratin. Dead keratinocytes secrete defensins, which are part of our innate immunity. In healthy skin, the densely packed lipid lamellae of the stratum corneum are held together by a strong network of multiple weak interactions: hydrogen bonds (H-bonds) in the headgroup region, van der Waals forces and hydrophobic interactions.

## Brief Characteristics of Absorption of Topical NSAIDs

A prerequisite for achieving effective concentrations of topically applied NSAIDs in the affected tissue or organ is their sufficient penetration through the skin. One of mechanism of absorption of active substances after topical application is passive diffusion driven by a concentration gradient, which is influenced by the chemical properties of both the active substance and the excipients. Rubbing or local heat can increase local blood flow and facilitates uptake of active substance into the blood, maintaining the concentration gradient that drives the passive diffusion. Also skin surface occlusion, which hydrates the stratum corneum, often facilitates penetration through the skin and into the underlying tissues. Repetitive administration can as well greatly increase the bioavailability of the drug (6). The absorption can be evaluated by several parameters: depth of absorption, rate of absorption (penetration) to the site of action, achieved maximum concentration at the site of action, etc (6). The important parameter is the achieved bioavailability at the site of inflammation, which is characterized by the index of topical anti-inflammatory activity (ITAA), expressed as the ratio of the achieved concentration to the concentration capable of inhibiting cyclooxygenase 2 (COX-2) by 50% (so-called  $IC_{50}$ ).  $IC_{50}$  values reflect the concentration of active substance required reducing COX-2 activity by 50% – a lower value indicates higher efficacy. In this respect, diclofenac is significantly more effective than ibuprofen, ketoprofen, indomethacin or nimesulide, respectively. COX-2 inhibits at the lowest con-

centrations compared to other commonly used NSAIDs (12). In general however, different NSAIDs achieve different penetration. The intensity of penetration of the active substance through the skin depends on lot of factors. The key factors influencing the extent and rate of NSAID penetration into its site of action are: molecular size, water solubility, acidity, physicochemical properties (such as capability for interactions with other molecules), salt, composition of the vehicle in which they are applied to the skin, use of a penetration enhancer or site of application (6, 10).

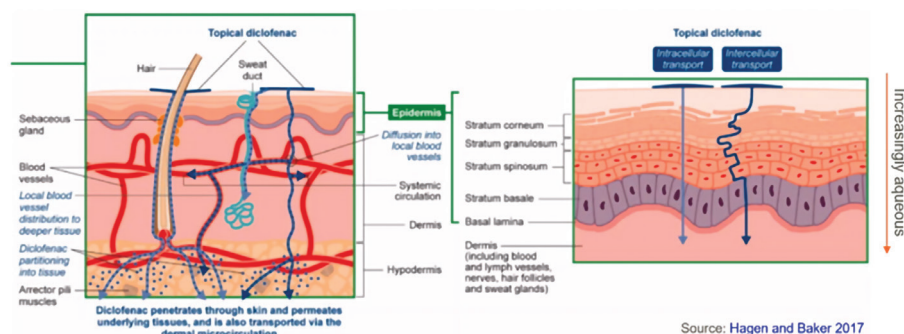
## Focus on Topical Diclofenac

The main advantage of topically administered NSAIDs is ease of application. The active substance hardly reaches the systemic circulation and therefore there is lower rate of systemic effects in the form of side effects and drug interactions.

Diclofenac is small molecule (296 g/mol), it is weak organic acid (pKa 3.9) that has both lipophilic and hydrophilic properties to be able to access all tissues (6). Diclofenac change to penetrates skin more extensively than several other NSAIDs (4).

From a pharmacokinetic point of view this is resulting in the absence of a first-pass metabolism. Clinical effect is evidenced, for example, by a meta-analysis of the Cochrane Library (5 311 participants with a topical NSAID, 3 470 with placebo, and 220 with an oral NSAID) with acute musculoskeletal pain (sprains, sports injuries) showing that topical NSAIDs provided good levels of pain relief in acute conditions such as sprains, strains and overuse injuries, probably similar to that provided by oral

**Fig. 1.** Major barrier to penetration of topical drugs is the stratum corneum – rate limiting step for epidermal drug transport



Source: Hagen and Baker 2017

Diclofenac transport is generally passive – i.e. from high concentration to low concentration (Fick's law).

NSAIDs (5). All of the above, like easy application, tolerability and clinical efficacy, are the essence of good patient compliance.

## Possibilities of Penetration Facilitation

In general, the penetration of active substance across the skin barrier can be promoted by chemical (enhancers) or physical (electroporation, iontophoresis, sonophoresis, microneedles, laser, etc.) means (8). Regardless of the chosen method, however, it is always necessary to respect the native condition of the skin, especially its hydration, the higher value of which significantly reduces the diffusion resistance.

If we focus on the possibility of using chemical penetration enhancers, then it is true for them that they should ideally be pharmacologically inactive and at the same time should not negatively affect the physiology of the skin for an extended period of time. Apart from their mechanism of action, it is to distinguish them according to their chemical structure. So far, lot of substances capable of potentiating penetration have been described, while the stronger but also weaker (especially irritation, hypersensitivity, risk of photosensitive reaction, etc.) aspects of individual representatives are evident (8). Ideally, the enhancer should be able to increase the penetration only selectively for the determined substance and, if possible, not significantly disrupt the skin barrier, or to allow its return ad integrum as soon as possible.

Well known enhancers include alcohols (ethanol, glycerol, etc.), fatty acids (oleic acid, linoleic acid, etc.), amines (diethanolamine), esters (isopropyl palmitate, isopropyl myristate, etc.), amides (dimethylacetamide, dimethylformamide, pyrrolidone derivatives, etc.), hydrocarbons (alkanes and squalene), surfactants (e.g. sodium laurate), terpenes (D-limonene, anise oil, etc.), sulfoxides (dimethyl sulfoxide) and phospholipids (lecithin) (8).

Penetration enhancers used in commercially available medicinal products in topical NSAID formulations include oleyl alcohol and oleic acid. While these molecules are chemically similar, the differences in some of their key molecular properties are significant and directly relate to how they interact with skin.

The two molecules have similar molecular weights and comprise identical lipophilic moiety (an oleyl chain). Oleic acid, however, has a bulkier polar headgroup compared to oleyl alcohol and can directly interact with skin lipids via multiple hydrogen-bonding interactions. In contrast, oleyl alcohol cannot interact with the skin barrier to the same extent because of its inability for multiple interactions (1). Oleic acid was however shown by IR imaging spectroscopy to diffuse laterally in stratum corneum, penetrate into the ordered lipid bilayers of the skin barrier, and alter the endogenous lipid structure (16). In a study by Boncheva and colleagues it was shown that the disruptive effect of oleic acid on skin barrier lipid organization was equivalent to increasing the stratum corneum lipids to a temperature of 50°C which represents significant barrier disruption (3). It is also noted in this work that another penetration enhancer, propylene glycol, causes far less disruption to the skin barrier, emphasizing again the aggressive nature of oleic acid as a penetration enhancer. Another publication demonstrated that the disruption of skin barrier function caused by oleic acid persisted for many hours after the molecule could no longer be detected in the outer stratum corneum. It was thus suggested that oleic acid remains deep in the stratum corneum where it continued to compromise skin barrier function for an extended period of time (13). Oleyl alcohol also penetrate into the skin however with reversible decrease of the barrier resistance (15).

In a study comparing various penetration enhancers, oleic acid had a higher enhancement ratio than oleyl alcohol (7).

But indeed, the use of two different penetration enhancers (oleic acid and oleyl alcohol) in topical NSAID products containing diclofenac showed that equivalent amounts of diclofenac penetrate through hu-

man skin *in vitro* (Public Assessment Report DE/H/5493+6245+6603/001-002/DC showing that generic product containing diclofenac 2% with penetration enhancer oleic acid and reference product containing diclofenac 2% with penetration enhancer oleyl alcohol are equivalent in *in vitro* penetration study determining and validating the method parameters and describing discriminatory power of the test method as well as in pivotal penetration study on industrial scale batches of generic product).

## Conclusion

Although we see the commercially available topical medicinal products today primarily by looking at the active substance, there is a clear need to always perceive their use in a broader context. In addition to the factors pertaining to the physiology of the skin, or factors on the patient's side, their final clinical effect is also considerably influenced by the formulation and excipients used. The above example shows that oleyl alcohol used as penetration enhancer has chemical properties which suggest a less disrupting effect on the skin barrier than the closely related penetration enhancer oleic acid while still opening the skin barrier to allow for effective delivery of diclofenac through the skin.

So even a small difference can have desired or unwanted consequences, which can affect the preference of one or another product.

## Declaration of interest

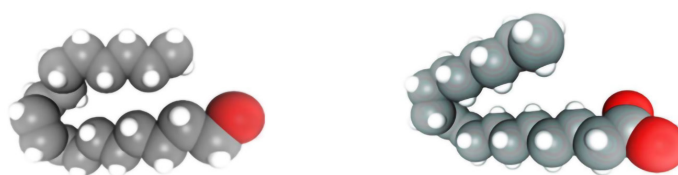
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## Data availability

*The data are available upon request from GlaxoSmithKline Consumer Healthcare.*

**Fig. 2.** 3D molecular representations of Oleyl Alcohol (left) and Oleic Acid (right) illustrating the considerable differences in their topological polar surface area and volume (data from PubChem)



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