

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 laureate), 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)

