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 concentrations 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).

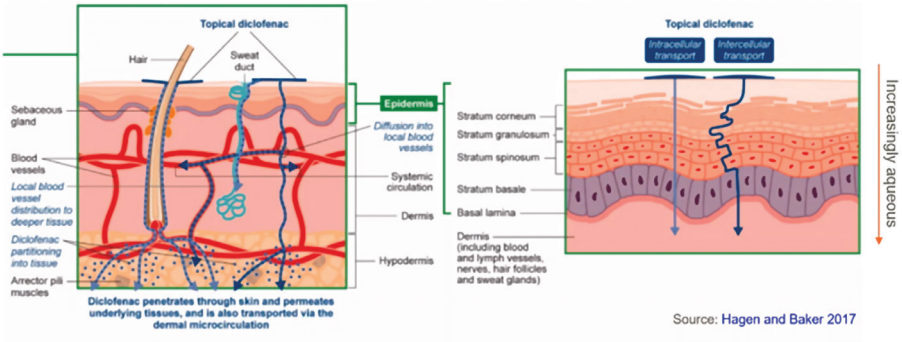
Focus on Topical Diclofenac

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*



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