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Topical Drug R&D using Open-Flow Microperfusion: Insights into Skin Biology

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ABSTRACT: Topical therapy requires drug molecules with very distinct properties, making topical drug development a high-risk and high-cost endeavor. At the level of the tight epidermal skin barrier, the drug needs to show ideal diffusive properties. Below the epidermal skin barrier, within the viable skin layers, at the level of its pharmacological targets, the drug needs to show distinct binding properties to prevent its fast clearance and thus be bioavailable in effective unbound drug concentrations that exceed the threshold for efficacy.

In vitro studies can verify envisaged delivery rates through the epidermal barrier. Only in vivo (animal) studies can verify both, the delivery and the resulting bioavailability at the target under treatment conditions and the effect of in vivo clearances. However, the state-of-the-art sampling method, punch biopsy, delivers a total tissue concentration, which significantly overestimates the pharmacological active drug concentration and thus is little helpful for drug candidate selection and de-risking the expensive clinical phases. The methodical limitations have been overcome by introducing the preclinical and clinical method of dermal open-flow microperfusion (dOFM), enabling a time-resolved measurement of total and unbound drug concentrations within dermal interstitial fluid under treatment conditions. These preclinical and clinical studies have provided a large dataset of intra-dermal concentration-time profiles from various topical drugs and formulations. Some aspects of the previously unknown kinetics witnessed at the site of action required an explanation, necessitating a deep dive into some “outdated” literature on skin permeation and into the subtleties of skin biology.

This presentation will show a number of dermal concentration-time profiles obtained by using dOFM in preclinical and clinical topical drug studies to discuss:

- The relationship between a drug’s molecular properties and its bioavailability in the skin
- The effect of drug binding on dermal unbound concentrations and clinical efficacy
- The effects of skin biology on the variability of topical permeation data
- The effects of male and female skin biology on topical permeation data