Transdermal Delivery of an Anti-inflammatory Peptide (KPV) across Dermatomed Human Skin, In Vitro

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Purpose
To optimize the in vitro transdermal delivery of an anti-inflammatory peptide, Lysine-Proline-Valine (KPV), using microporation, iontophoresis and their combination.

Methods
Transdermal delivery of KPV across dermatomed human skin was studied using Franz diffusion cells. Iontophoresis and microneedles were applied either individually or in combination to enhance KPV permeation. A validated, stability indicating HPLC assay was used to quantify KPV retention in the skin and permeation samples. Fluorescein isothiocyanate (FITC) conjugated KPV with confocal microscopy imaging was used to determine the KPV permeation pathways across the skin. Effect of various iontophoretic parameters (current density, current application time, KPV concentration) was investigated on KPV delivery across the skin treated with and without microneedles.

Results
No detectable level of KPV permeation across the intact skin by passive delivery was observed. The permeation remained low (4.42 ± 0.11 µg/cm²/h) even after pretreatment using microneedles. Application of iontophoresis (0.5 mA/cm²) enhanced the KPV permeation by 5-fold when compared to microneedle pretreatment. A synergistic effect for KPV permeation was noted when iontophoresis was used in combination with microneedles. The combination resulted in about 19-fold higher KPV permeation as compared to microneedles alone. The KPV delivery also could be modulated by altering the current density, duration of current application and drug concentration. A linear correlation was observed between KPV flux and donor KPV concentration or duration of current application. Further, the skin permeation data showed direct correlation with KPV skin deposition levels and donor concentration, current or duration of application. Confocal microscopy indicates that FITC tagged KPV has the fluorescence intensity up to a depth of 108 µm across the microneedle pretreated skin. However, fluorescence was confined to superficial layers and could be seen only up to a depth of 36 µm in case of passive delivery.

Conclusion
The transdermal delivery of KPV across human skin could be enhanced and optimized using microneedles, iontophoresis and their combination.