Assessment of Dermal Disposition in Skin: A Microdialysis Approach and Its Application in Developing In Vitro/In Vivo Correlation (IVIVC) for Topical Dermatological Drug Products (TDDP)

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Purpose
To explore the possibility of using dermal microdialysis as a potential tool to develop IVIVC for TDDP that act locally in dermis. Specifically, the project consists of two parts, (i) development of a novel method to estimate dermal disposition function (UIR - Unit Impulse Response) using dermal microdialysis and (ii) validation of proposed approach, using estimated disposition function to predict the in-vivo dermal drug concentration from in-vitro permeation data following topical dermatological administration. In the present study, Diphenhydramine hydrochloride (DPH), a classic antihistamine was used as a model drug because of its extensive topical use for various dermatological indications.

Methods
For the quantitative analysis of DPH, appropriate validation procedures were performed to confirm the reliability and reproducibility of the optimized reverse phase HPLC method. Preliminary in-vitro and in-vivo studies were performed to assess the feasibility of using microdialysis technique to estimate dermal disposition of DPH in rabbits. For in-vivo dermal disposition studies, three linear microdialysis probes were implanted in parallel into the shaved dorsal region of rabbit. The central probe was used for dermal DPH delivery and the two lateral probes were used for dermal DPH sampling. Disposition studies were performed in replicates at six different DPH dermal doses. The obtained dermal DPH concentrations versus time data were analyzed by Non-compartmental analysis (NCA) to assess the UIR.

The in-vitro permeability and in-vivo dermal exposure experiments were performed to develop IVIVC using four different DPH gels, 2.0% Benadryl brand (Gel A), 2.0% CVS generic (Gel B), 3.5% (Gel C) and 5.0% (Gel D) (Gel A and B commercial formulations, Gel C and D compounded formulations). The characterization of all gels were performed by assessing product quality attributes such as content uniformity, viscosity, pH and physical appearance. The product performance was evaluated by in-vitro release tests (IVRT) and in-vitro permeation tests (IVPT) to assess the drug release from all the gels. The IVRT and IVPT were performed in vertical Franz cell assembly using synthetic cellulose and porcine ear skin membrane as diffusion barrier, respectively. Following topical application of all DPH gels, in-vivo dermal absorption studies were performed using microdialysis technique in rabbits.

For the Level A IVIVC, the numerical convolution approach was used to predict the point-to-point in-vivo dermal concentration of DPH from IVPT and UIR data, while the in-vivo absorption rate of DPH was estimated using model independent numerical deconvolution method. The in-vivo absorption data was graphically compared to in-vitro permeation data by Levy plot. For the Level C IVIVC, in-vitro flux and in-vivo Clearance estimates were used to predict in-vivo steady state dermal DPH concentration.

Results
The observed dermal pharmacokinetic was indeed linear. The dermal Volume of distribution (Geo. mean range 111.12 to 231.18 ml) and Clearance (Geo. mean range 1.23 to 2.12 ml/min) estimates were consistent across different DPH doses. The results from the characterization tests were consistent across different gels. The estimated in-vitro steady state flux values (Mean ± SD) for the gel A, B, C and D from IVRT studies were 521.40 ± 93.81, 500.11 ± 68.01, 1102.33 ± 114.39 and 1684.67 ± 178.66 μg/(cm²*hr) respectively. The observed in-vitro steady state flux estimates (Mean ± SD) for gel A, B, C and D from IVPT were 183.73 ± 9.87, 178.54 ± 7.13, 236.68 ± 9.06 and 342.00 ± 32.92 μg/(cm²*hr) respectively. Similarly, the observed in-vitro flux estimates (Mean ± SD) for gel A, B, C and D were 5.97 ± 1.39, 5.21 ± 1.05, 11.41 ± 1.96 and 16.03 ± 4.92 μg/(cm²*hr) respectively. The observed in-vivo flux on comparison with in-vitro flux at different concentration of DPH gel showed a linear correlation (R² > 0.93). The results show that the simulated point-to-point and steady state dermal DPH concentrations following topical application, as estimated by Level A and Level C IVIVC approach were overestimated, as compared to actual observed DPH data. The observed differences between the actual and predicted data might be due to the differences between the skin membranes. However, for the Level C IVIVC, the scaling factor between observed and predicted values was similar across all the experiments suggesting that the approach may still have predictive capability.

Conclusion
The development of IVIVC for TDDP is an evolving concept and this project explores a new application of dermal microdialysis in developing IVIVC for TDDP. The findings from this study strongly suggest that in-vitro permeation test complemented with microdialysis based in-vivo dermal disposition studies can be developed as a potential useful tool to establish IVIVC for topical dermatological drug products.