Deciphering the Effects of Microstructure on Lidocaine-Prilocaine Topical Product Performance

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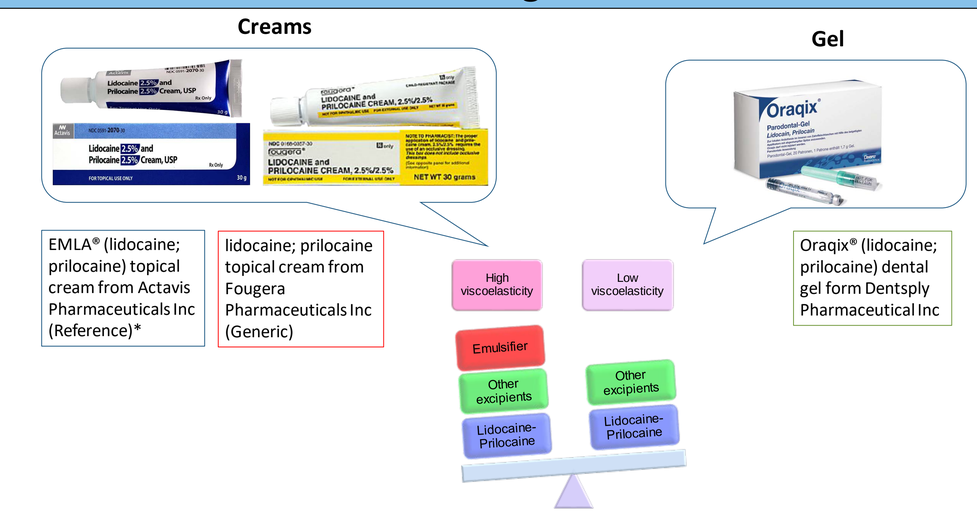
Background



Topical cream and gel products containing both lidocaine (2.5%) and prilocaine (2.5%) have an eutectic mixture of these drugs in a 1:1 ratio w/w that forms a dispersed phase in the product. These products are available as creams and gels. The lidocaine prilocaine creams are composed of polyoxyethylene fatty acid esters as emulsifiers whereas the lidocaine prilocaine gel is mostly aqueous consisting of a mixture of poloxomers as polymerizing agents and therefore, has different physical and structural properties than the cream products. We characterized and compared the physical and structural properties of the lidocaine prilocaine cream and gel products, as well as the cutaneous pharmacokinetics (PK) of both drugs using an in vitro permeation test (IVPT) to elucidate how physicochemical differences between the cream and gel alter the bioavailability of each active ingredient from the products.

* According to the Orange Book, currently the reference product is owned by Teva Branded Pharmaceutical Products R&D, Inc.

Methodology

❑ Loss of water and volatiles

A dose of approximately 10 mg/cm^2 was spread on a glass slide and they were placed on a heating pad at 35°C and the products were allowed to dry naturally. The weight loss was recorded at different time points and the cumulative loss (mg) for each product was determined.

❑ Rheological behaviour

Rheological assessment by shear stress sweep testing was performed on an AR-G2 Rheometer (TA Instruments, New Castle, DE) fitted with a smart swap Peltier plate. The A 40 standard steel parallel plate was used with a gap height of 500 µm and both the upper and lower plates were covered with sandpaper (P180) to prevent the products from slipping.

❑ *In vitro* permeation testing using human excised skin

IVPT studies were performed on six skin donors with six replicates per donor using heat separated human epidermis and a flow through diffusion system (PermeGear®, Hellertown, PA). Figure 1 describes the various steps in the IVPT studies.

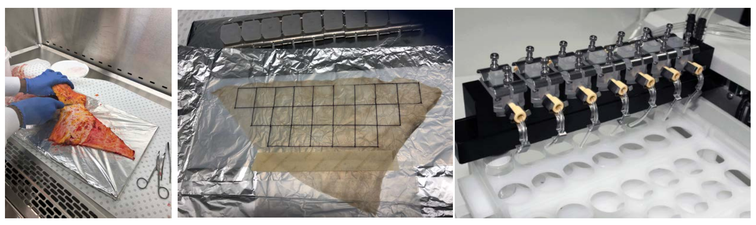


Figure 1: Experimental set-up for IVPT experiments

❑ Cutaneous pharmacokinetic (PK) assessment

Drug retention in the stratum corneum was assessed by tape stripping with D101 D-Squame® stripping discs (Clinical & Derm LLC, USA) for up to 20 tape strips (Figure 2). The drug was extracted from the swabs, tape strips and the remaining epidermis using 100% methanol by stirring at 200 rpm overnight (15-18 hrs). The drug concentration in all the samples was analyzed using high performance liquid chromatography (HPLC).

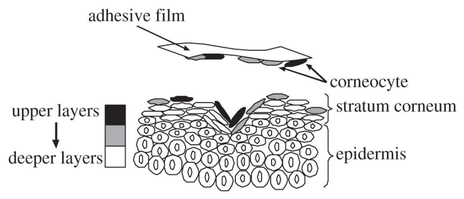


Figure 2: Sequential tape stripping for pharmacokinetic (PK) assessment of stratum corneum drug levels

❑ Examination of internal microstructure with electron microscopy

JOEL scanning electron microscope (JSM7100F) equipped with a secondary electron detector was used for morphological examination. The samples were loaded on the cryo-specimen holder and cryo-fixed in slush nitrogen and/or high pressure freezing (HPF), then quickly transferred under vacuum to the cryo-preparation chamber in the frozen state. The frozen cream samples were fractured using an in-built fracture blade and then sputter coated. The coated samples were moved to the imaging chamber equipped with an anti-contaminator.

Acknowledgment

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Results

The evaporative rate, rheological results, and cutaneous PK of lidocaine and prilocaine were comparable for the reference and generic creams. By contrast, compared to the creams, the gel's evaporative rate was substantially higher, its shear stress trend was substantially lower, and the cutaneous PK endpoint of lidocaine and prilocaine, e.g., maximum flux (J_{max}) and area under the curve (AUC) were substantially lower. Despite the relatively small number of donors, the creams were found to be bioequivalent (BE) for J_{max} and AUC for both drugs, except when comparing the cumulative amount permeated for prilocaine. The gel was found to be not bioequivalent to the reference cream for any PK endpoint for either drug (Table1). The scaled average BE (SABE) analysis provided greater statistical power than the average BE (ABE) analysis (Figure 9).

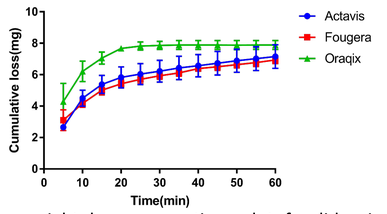


Figure 3: Cumulative weight loss versus time plot for lidocaine-prilocaine topical formulations at 32°C (skin temperature) on glass slides by gravimetric analysis (n=3). Data are expressed as Mean ± SD.

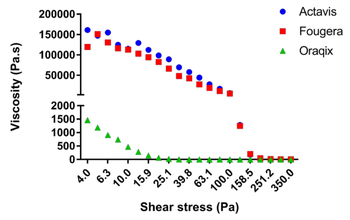


Figure 4: Viscosity as a function of shear stress for all three test products (n=3). Data are expressed as Mean ± SD.

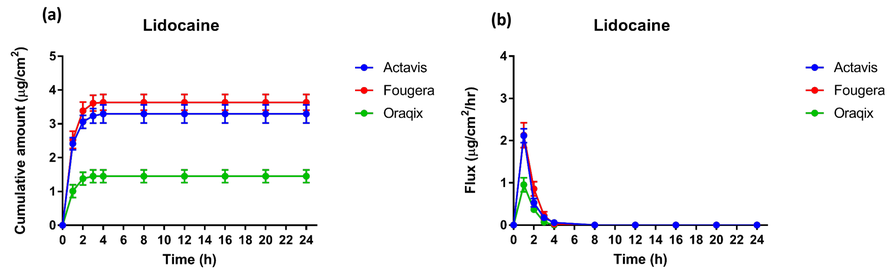


Figure 5: *In vitro* permeation profile of lidocaine from applied products on human epidermal membranes: (a) Cumulative amount (µg/cm^2) and (b) Flux (µg/cm^2/h) versus time. Data are expressed as Mean ± SEM from six donors and six replicates.

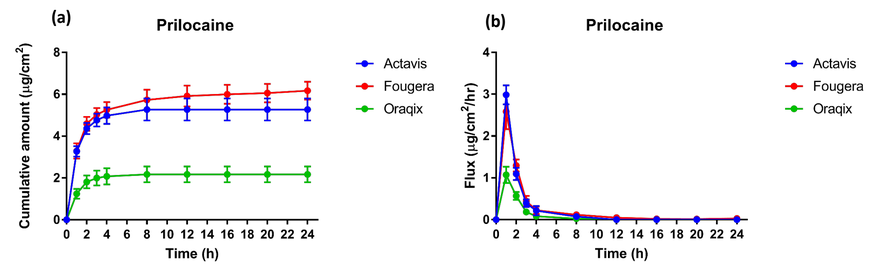


Figure 6: *In vitro* permeation profile of prilocaine from applied products on human epidermal membranes: (a) Cumulative amount (µg/cm^2) and (b) Flux (µg/cm^2/h) versus time. Data are expressed as Mean ± SEM from six donors and six replicates.

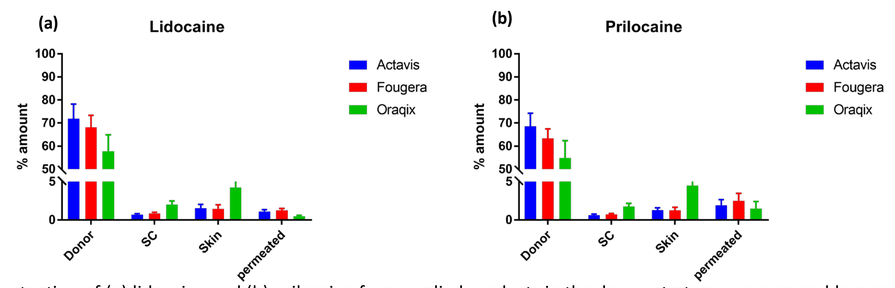


Figure 7: Distribution and retention of (a) lidocaine and (b) prilocaine from applied products in the donor, stratum corneum and human epidermal membranes. Results are expressed as a percentage of the applied dose (Mean ± SEM, n = 6, six donors).

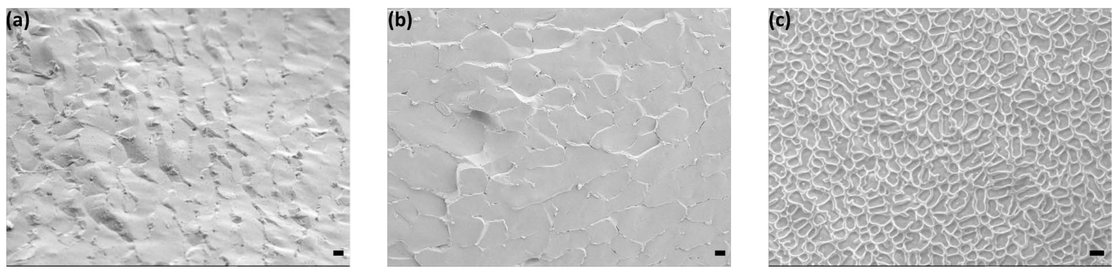


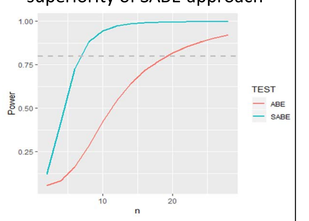
Figure 8: Cryo-SEM images at 3000X depicting the internal microstructures of (a) Actavis cream (b) Fougera cream and (c) Oraqix gel. Scale bar - 1µm

Tables 1: BE analysis results for lidocaine; prilocaine products, comparison and pharmacokinetic parameters for lidocaine (on the left) and prilocaine (on the right)

Comparison	Parameter	Between Donor SD	Swr	Point Estimate GMR	SABE UCB	ABE CI	BE
FOUGERA vs ACTAVIS	AUC	0.19	0.526	1.009	-0.15		✓
	Cmax	0.11	0.260	1.084		(0.99,1.19)	✓
ORAQIX gel vs ACTAVIS	AUC	0.32	0.526	0.491	0.73		✗
	Cmax	0.30	0.260	0.410		(0.32,0.53)	✗

Comparison	Parameter	Between Donor SD	Swr	Point Estimate GMR	SABE UCB	ABE CI	BE
FOUGERA vs ACTAVIS	AUC	0.2877	0.4622	0.8169	0.0308 -0.0679 (1.33)		✓
	Cmax	0.1603	0.3045	1.1156	-0.0106		✓
ORAQIX gel vs ACTAVIS	AUC	0.2427	0.4622	0.3599	1.3252		✗
	Cmax	0.2695	0.3045	0.3631	1.4513		✗

Figure 9. Statistical power for lidocaine AUC showing superiority of SABE approach



Discussion and Summary

These results demonstrate the impact of the formulation composition and the arrangement of matter on drug product's performance. Due to its largely aqueous nature, the rate of evaporation and, hence, the water loss were higher from the gel compared to the creams (Figure 3). Similarly, the viscosity of the gel was found to be considerably lower than that of the creams (Figure 4). The skin permeation (cumulative amount and flux) of lidocaine and prilocaine was similar between the two creams, whereas permeation of the two active ingredients was significantly lower from the gel (Figures 5 and 6). Due to lower viscosity and different composition, the active ingredients have faster and or higher partitioning from the vehicle into the skin for the gel product compared to the cream. Also, it is possible that the partitioning of the excipients to the upper layers of skin can play a role in retaining the drugs in the skin for the gel product compared to the cream (Figure 7). However, the amount permeated over a larger time scale was higher from the cream formulations, highlighting the role of emulsifiers and solubilizers in driving skin penetration. The gel is composed of thermoreversible polymers which tend to form a low viscosity gel as the temperature increases beyond 32°C. The above differences point to alterations in the internal microstructure as visualized by cryo-SEM. Polymer structure was visible in the gel and the cream microstructure was dominated by lamellar arrangement which is analogous of emulsifiers (Figure 8). Despite slight compositional differences, the structural properties and cutaneous PK of the creams are comparable for lidocaine and prilocaine. By contrast, the gel has a fundamentally different arrangement of matter than the creams and, consequently, also exhibits a different cutaneous PK for both active ingredients.