Correlation of Physico-Structural (Q3) Properties of Lidocaine/Prilocaine Topical Products with Product Performance In Vitro and In Vivo

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PURPOSE

In the past few years, a collective weight of evidence approach has been recommended to support a demonstration of bioequivalence (BE) for several topical drug products. An essential component of this approach is a comprehensive characterization of the physico-structural (Q3) properties of complex topical semisolid dosage forms. The purpose of this study was to determine if comparative Q3 characterization of topical lidocaine and prilocaine products may be used to predict the comparative product performance, which was evaluated by comparing the cutaneous pharmacokinetics (PK) of lidocaine and prilocaine in vitro and in vivo.

OBJECTIVES

- Characterize and compare the Q3 properties of cream and gel products, each containing both lidocaine and prilocaine
- Compare the performance of lidocaine/prilocaine cream and gel products using in vitro and in vivo cutaneous PK studies

METHOD(S)

The products evaluated in this study were 1) the reference product, EMLA® (lidocaine; prilocaine) topical cream, 2.5%;2.5% 2) a generic version of EMLA® cream, and 3) Oraqix® (lidocaine; prilocaine) dental gel, 2.5%;2.5% as a different formulation with the same strength of lidocaine and prilocaine. The comparative Q3 assessment of these three drug products included microscopic examination, pH, evaporative rate, and rheological behavior. The cutaneous PK of lidocaine and prilocaine from the gel and cream products were compared by an in vitro permeation test (IVPT) with a replicate study design (six skin donors with six replicates per donor) using heat separated human epidermis and a flow through diffusion system. The BE of the generic cream and of Oraqix® gel to EMLA® cream was evaluated based upon cutaneous PK endpoints for both lidocaine and prilocaine, using a reference scaled average BE (SABE) analysis and evaluation of the 90% confidence interval (CI). The dermal bioavailability of EMLA® and Oraqix® was also compared in an in vivo pilot study using dermal open flow microperfusion (dOFM) in 6 healthy subjects. The dose of all products used in the IVPT and dOFM studies was 10 mg product/cm^2.

RESULT(S)

Quality tests and Q3 properties

The Q3 properties of the reference and generic lidocaine and prilocaine topical creams were similar to each other and different that those of Oraqix® gel:

- The average pH values measured for the reference lidocaine/prilocaine cream, the generic lidocaine/prilocaine cream, and Oraqix® gel were 9.10, 8.90 (i.e., 9.0 ± 0.1) and 7.65, respectively.
- The microscopic images of the cream products showed the presence of globules with a diameter of 1-3 µm, while the Oraqix® gel appeared to be a homogenous globule-free system. The cream products also showed a different microstructure than the gel product under cryo-scanning electron microscopy (cryo-SEM) (Figure 2).

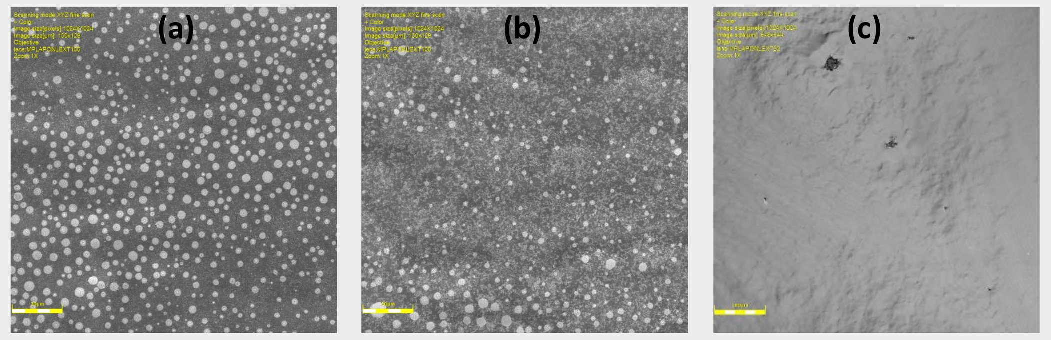

Figure 1. *Light microscopy images: (a) EMLA® cream and (b) generic lidocaine and prilocaine cream showing globules, vs. a homogenous globule-free matrix in the (c) Oraqix® gel. The scale bars are 20 µm in images a and b, and 100 µm in image c.*

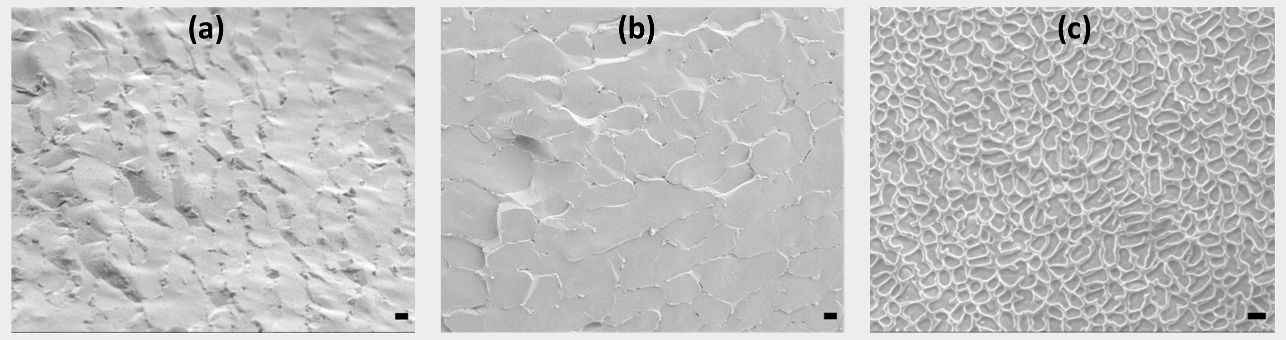

Figure 2. *Cryo-SEM images at 3000X magnification depicting the internal microstructures of (a) EMLA® cream (b) generic lidocaine prilocaine cream and (c) Oraqix® gel. Scale bar - 1µm*

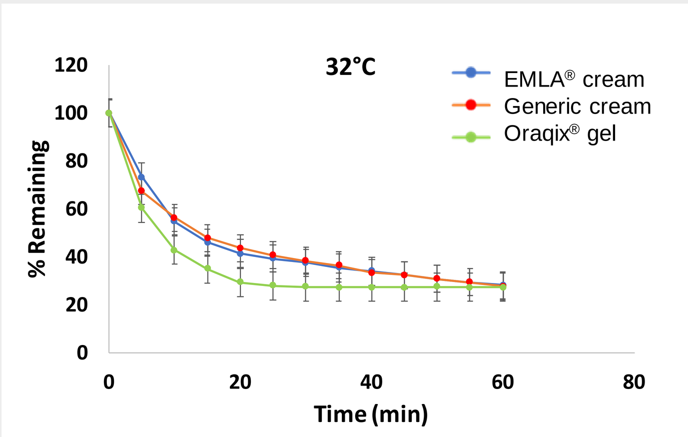

Figure 3. *Rate of evaporation of volatile components from lidocaine; prilocaine topical cream and gel products measured gravimetrically at 32ºC. Data are expressed as Mean ± SD (n=3).*

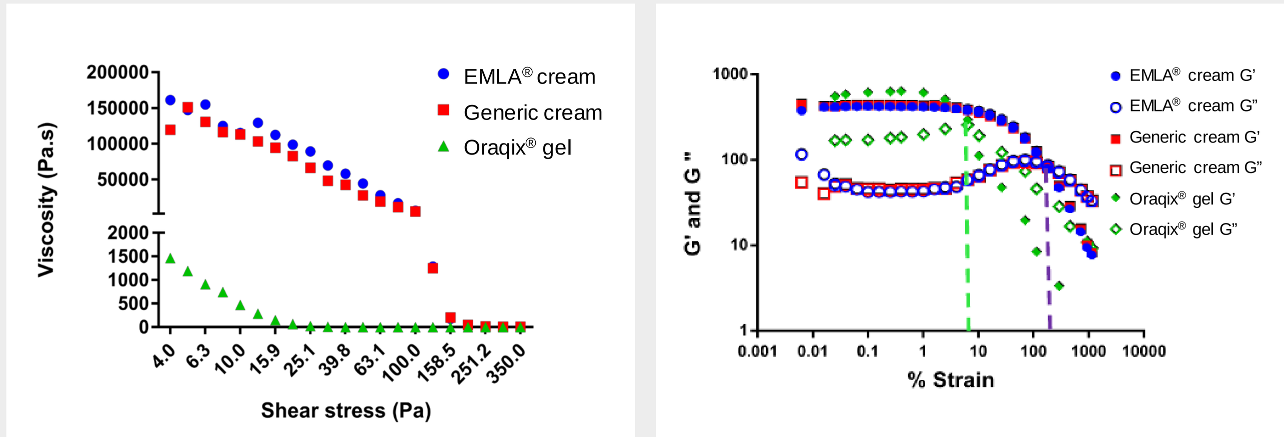

Figure 4. Left: *Viscosity as a function of shear stress for lidocaine and prilocaine cream and gel products.* **Right:** *Strain sweep for all three products. Closed symbols (G') represent the storage modulus and the open symbols represent loss modulus (G''). The yield stress was determined to be 110 for the cream products and 11 for Oraqix® gel.*

Performance tests

1. In vitro cutaneous PK study using IVPT

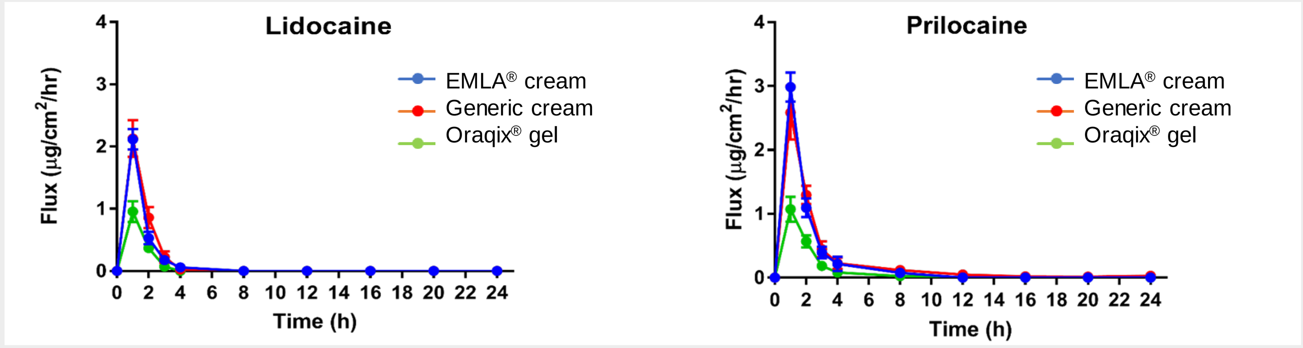

Figure 5. *Cutaneous PK (flux profile) of lidocaine and prilocaine in vitro from topical applications of the same dose of EMLA® cream, the generic cream, and Oraqix® gel. Data are shown as Mean ± SEM from 6 donors and 6 replicates.*

Table 1. *BE analysis results for lidocaine (in orange); prilocaine (in yellow) based on PK endpoints of area under the curve (AUC) and maximum flux (J_{max}).*

Comparison	Parameter	Between Donor SD	Swr	Point Estimate GMR	SABE- Upper Bound of 95% CI	ABE – 90% CI	BE
Generic cream vs EMLA® cream	AUC	0.19	0.526	1.009	-0.15		✓
	J_{max}	0.11	0.260	1.084		(0.99,1.19)	✓
Oraqix® gel vs EMLA® cream	AUC	0.32	0.526	0.491	0.73		✗
	J_{max}	0.30	0.260	0.410		(0.32,0.53)	✗
Generic cream vs EMLA® cream	AUC	0.2877	0.4622	0.8169	0.0308 (borderline)		(✓)
	J_{max}	0.1603	0.3045	1.1156	-0.0106 (borderline)		✓
Oraqix® gel vs EMLA® cream	AUC	0.2427	0.4622	0.3599	1.3252		✗
	J_{max}	0.2695	0.3045	0.3631	1.4513		✗

2. In vivo cutaneous PK study using dOFM

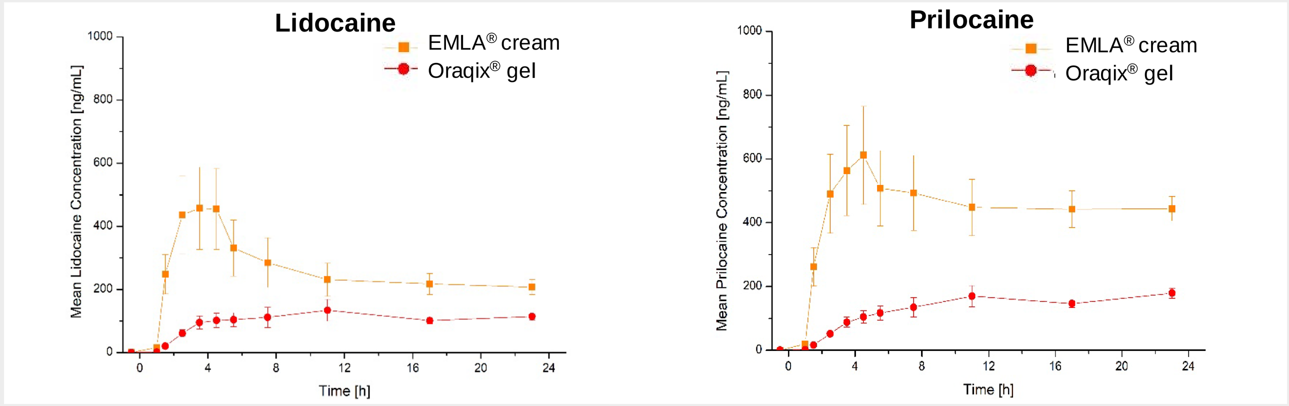

Figure 6. *Mean lidocaine and prilocaine concentration-time profiles (±SE) for EMLA® cream and for Oraqix® gel following application of 10 mg/cm^2 of products. Data are shown as Mean ± SEM from six subjects.*

CONCLUSION(S)

These results demonstrate the correlation between the Q3 similarities (or differences) of three comparator products and the their corresponding cutaneous PK, both in vitro (IVPT) and in vivo (dOFM). The similarity of Q3 characteristics between the reference and generic creams accurately correlated with and was predictive of comparable bioavailability (and bioequivalence) for both lidocaine and prilocaine between the two creams, with the exception of prilocaine AUC in the (underpowered) IVPT study. The difference in Q3 characteristics between the reference cream and the gel accurately correlated with and was predictive of differences in bioavailability.

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