Method Development and Optimization of an *In Vitro* Permeation Test (IVPT) to Compare the Rate and Extent of Drug Permeation from Topical Drug Products

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PURPOSE & OBJECTIVE

An *in vitro* permeation test (IVPT) using excised human skin can be a useful methodology to compare the cutaneous bioavailability of drugs from topical dermatological drug products, and may be able to support a demonstration of bioequivalence (BE) in certain cases. There are several study design parameters that may be critical for such IVPT studies, like the IVPT apparatus, type of skin, receptor solution, study duration, dose application technique, etc. One of the most important parameters to validate is the amount of product applied which must be selected to ensure that the resulting IVPT method remains sensitive to differences (particularly increases) in topical bioavailability (BA). Another important consideration is the sampling schedule, which must be selected to ensure that a sufficiently complete cutaneous pharmacokinetic (PK) profile is captured, with sufficient resolution to characterize the cutaneous PK endpoints of maximum flux (J_{max}) and cumulative amount permeated (AUC).

METHOD(S)

A topical cream containing both lidocaine and prilocaine (2.5%; 2.5%) was used in the study. The IVPT studies were conducted using Franz diffusion cells with an active diffusional area of 2cm^2, with dermatomed (posterior torso) human cadaver skin from a single donor (acquired from New York Firefighters Skin Bank), with 6 replicates per study condition. The receptor medium consisted of phosphate buffered saline (pH 7.4) with 0.01% gentamicin sulfate. An anticipated target dose for the IVPT method was 10 mg/cm^2. Data are presented as mean ± std.

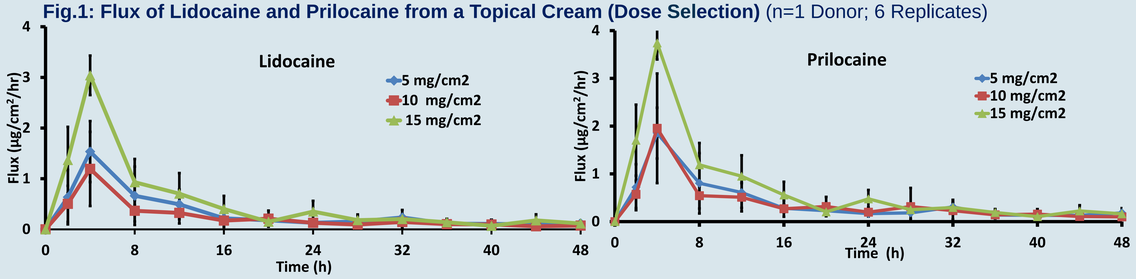
Study I (dose selection): Sensitivity of the IVPT method to increases or decreases in BA, was performed using 5 mg/cm^2, 10 mg/cm^2, or 15 mg/cm^2 of the cream; sampling was performed at 2 hour intervals for the first 4 hours and then at 4 hour intervals up to 48 hours.

Study II (study duration and sampling frequency): Three independent IVPT studies were performed to optimize the duration and sampling frequency. The sampling schedules explored were i) 2 hour intervals for 0 to 48 hours; ii) every half hour intervals for 4 hours; or iii) 1 hour intervals for the first 4 hours and 4 hour intervals from 4 to 24 hours.

The cutaneous PK endpoints, J_{max} and AUC were essential parameters needed to characterize and compare the dynamic rate (flux profile) and extent of BA for lidocaine and prilocaine.

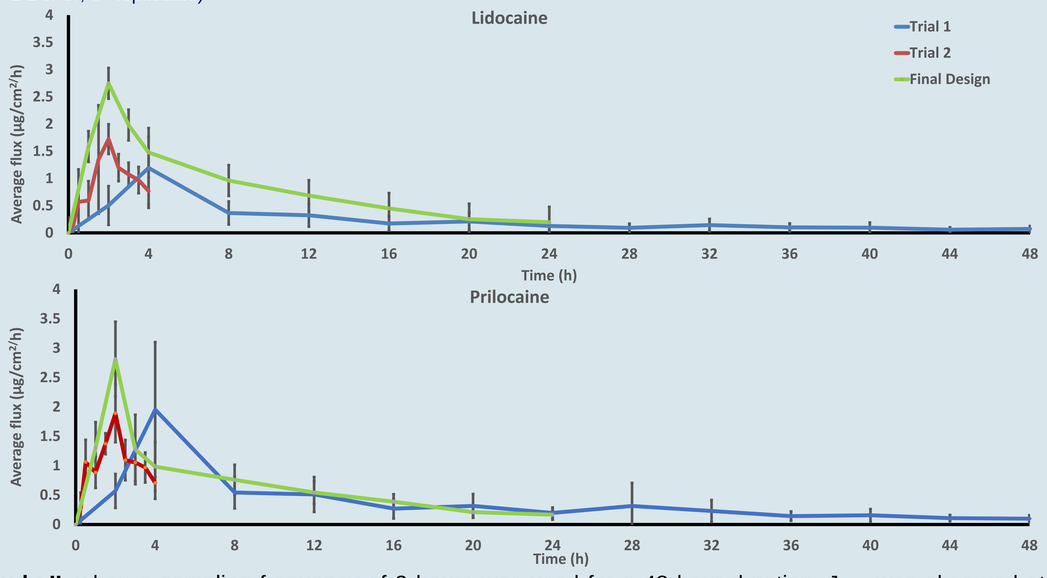
RESULT(S)

Fig.1: Flux of Lidocaine and Prilocaine from a Topical Cream (Dose Selection) (n=1 Donor; 6 Replicates)



In study I, the J_{max} and AUC values obtained at the high dose of 15 mg/cm^2 were consistently discriminated from those for the target 10 mg/cm^2 dose, indicating that an IVPT method using that target dose would still be able to discriminate increases in the rate and extent of bioavailability for both lidocaine and prilocaine. The low dose of 5 mg/cm^2 was not as well discriminated from the target 10 mg/cm^2 dose.

Fig.2: Flux of Lidocaine and Prilocaine from a Topical Cream (Optimizing Study Duration and Sampling Frequency) (n=1 Donor; 6 Replicates)



In study II, when a sampling frequency of 2 hours was used for a 48 hour duration, J_{max} was observed at the first sampling point (2 h) which suggested a potentially inadequate resolution of the early PK profile (Trial 1). When higher resolution sampling was conducted at 30 minute intervals for the first 4 hours, a gradual increase in the flux was observed at all time points and J_{max} was confirmed to truly be at 2 hours (Trial 2). When the sampling schedule was optimized to 1 hour intervals for the first 4 hours and 4 hour intervals from 4 to 24 hours, both the cutaneous PK parameters, J_{max} and AUC, were able to be adequately characterized (Final Design).

CONCLUSION(S)

The results of this study illustrate how to efficiently optimize key study parameters during IVPT method development, in order to identify conditions for a sensitive and discriminating IVPT study that can appropriately characterize the cutaneous PK endpoints of J_{max} and AUC. The modulation of the applied dose is an efficient way to evaluate the sensitivity of an IVPT method to changes in bioavailability. The underlying principle is that, when the dosage form is reasonably volatile, changes in the dose amount (volume) may be expected to lead to changes in drug delivery because the metamorphosis of the applied product (as it dries on the skin) alters the delivery of the drug into the skin. Smaller amounts dry more quickly, and may not be able to deliver drug into the skin for very long, which may reduce bioavailability (although the rapid changes in thermodynamic activity during drying may also briefly enhance drug delivery). Conversely, larger amounts dry more slowly, and the product can continue to deliver drug into the skin for longer, resulting in a greater rate and extent of permeation. The specific smaller and larger dose amounts that can provide discriminated flux profiles may be formulation dependent, and this strategy may not be effective for non-volatile dosage forms.

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