Evaluation of Diclofenac Epolamine 1.3% and Lidocaine 5% Topical Patches by Dermal Pharmacokinetic Methods: *In Vitro* Tape Stripping and *In Vitro* Permeation Testing (IVPT)

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Introduction

For topical drug products where the site of action is in the skin or in nearby surrounding tissues, the local bioavailability of the drug may be more directly relevant to efficacy and bioequivalence. Two methods of importance are *in vitro* tape stripping and *in vitro* permeation testing (IVPT). Tape stripping is used to quantify drug amounts in the stratum corneum (SC), while IVPT is used to characterize the permeation profile of drugs through the skin. Currently there is no standard for determining bioavailability for topical formulations. The combination of these two methods could provide complementary information about the bioavailability and potential bioequivalence of topical formulations.

Objective

Two dermal pharmacokinetic methods (IVPT and *in vitro* tape stripping) were studied in parallel to evaluate their utility for topical bioavailability assessment. Due to their differing physicochemical properties, lidocaine and diclofenac were used as model topical compounds.

Methods

Study Design

Lidocaine 5% and diclofenac epolamine 1.3% patches (0.95 cm^2) were applied to porcine skin mounted on flow-through diffusion cells containing isotonic phosphate buffer (pH 7.4) as the receiver solution. Drug was applied to the skin for a specified uptake time, after which it was removed and drug levels in the skin determined either immediately (uptake measurement) or after a clearance time (clearance measurement). Multiple IVPT and *in vitro* tape stripping studies were conducted with varying uptake and clearance time points. For the lidocaine patch the study was conducted over 24 hours with 8, 12 and 16 h uptake time with 16, 12 and 8 h clearances respectively. For the diclofenac patch the study was conducted over varying hours with 12 h uptake and 12, 24, and 72 h clearances.

In Vitro Permeation Test

Receiver solution samples were collected every 2 to 3 h. The IVPT samples were analyzed using ultra performance liquid chromatography (UPLC).

Tape Stripping

The mass of skin on each tape was determined by weighing before and after tape stripping. Successive tape strips were combined into groups with a combined SC weight of at least 400 µg. Lidocaine or diclofenac were extracted from each group of tapes and from the skin section remaining after tape stripping using 3 mL methanol and shaking in 15 mL centrifuge tubes for 20 h. The extracts from the tape strips and remaining skin were analyzed using UPLC.

Analytical Method

An Agilent ZORBAX 300SB-C8 (3.5 µm, 4.6 x 150 mm) column with a Phenomenex SecurityGuard™ C18 cartridge (5 µm, 4 x 3.0 mm) was used for the analytical method for IVPT samples and tape stripping samples for both lidocaine and diclofenac. The mobile phase composition used for lidocaine was (A):acetonitrile, (B):50 mM phosphate buffer (pH 5.9); isocratic conditions (A:20, B:80, v/v) at a flow rate of 1.0 mL/min. An injection volume of 10 µL was used for all samples. The mobile phase composition used for diclofenac was (A):methanol, (B):20 mM phosphate buffer with TFA (pH 2.3); isocratic conditions (A:65, B:35, v/v) at a flow rate of 1.0 mL/min. An injection volume of 10 µL was used for all samples.

Results

Table 1. Differences in physicochemical properties between lidocaine and diclofenac

	Lidocaine	Diclofenac
Skin Permeation	High	Low
Protein Binding	Low	High
Water Solubility (mg/L)	4100 (30 °C)	2.37 (25 °C)
LogP	2.44	4.51
pKa	8.01	4.15

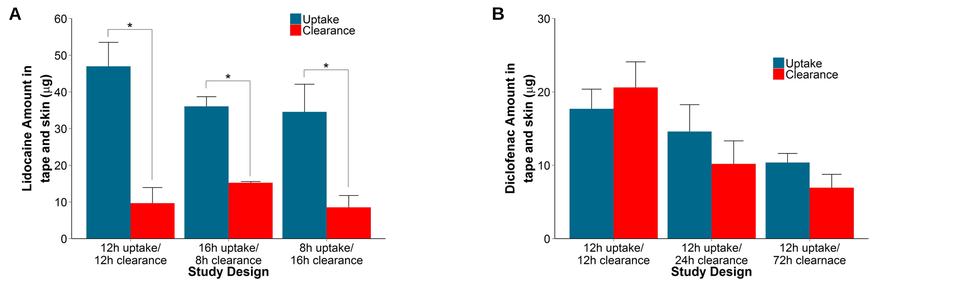

Figure 1. Amount after uptake and clearance in tape strips and porcine skin piece left after tape stripping: (A) lidocaine and (B) diclofenac (n=3 per uptake and clearance) [* represents significantly different].

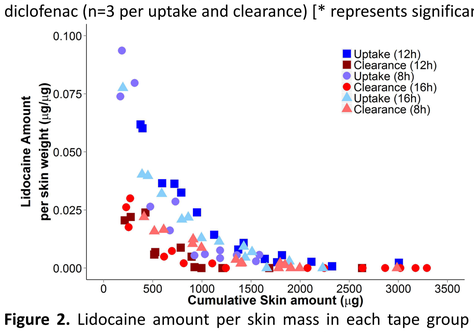

Figure 2. Lidocaine amount per skin mass in each tape group versus cumulative skin mass from three different study designs for Lidocaine patch: 1) 12 h uptake and 12 h clearance phase, 2) 8 h uptake and 16 h clearance phase, and 3) 16 h uptake and 8 h clearance phase

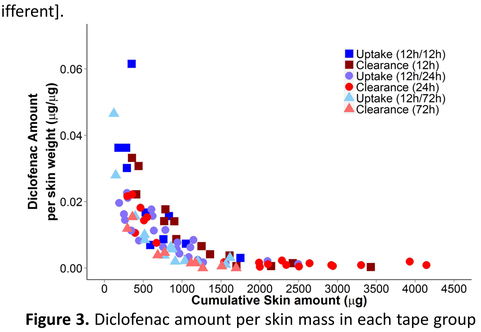

Figure 3. Diclofenac amount per skin mass in each tape group versus cumulative skin mass from three different study designs for diclofenac patch applied for 12 h followed by a: 1) 12 h clearance phase, 2) 24 h clearance phase, and 3) 72 h clearance phase

Table 2. Total permeation and drug amount from tape strips and skin samples left after tape stripping for 12 h uptake: A) lidocaine patch with 12 h clearance, and B) diclofenac patch with 24 h clearance [values reported as mean ± SD].

	Lidocaine Patch		Diclofenac Patch	
	Total permeation (µg)	Skin lidocaine amount (µg)	Total permeation (µg)	Skin diclofenac amount (µg)
Uptake	127.0 ± 41.7	47.0 ± 6.5	10.0 ± 4.2	14.6 ± 3.7
Clearance	160.9 ± 50.4	9.7 ± 4.2	11.7 ± 3.3	10.2 ± 3.2

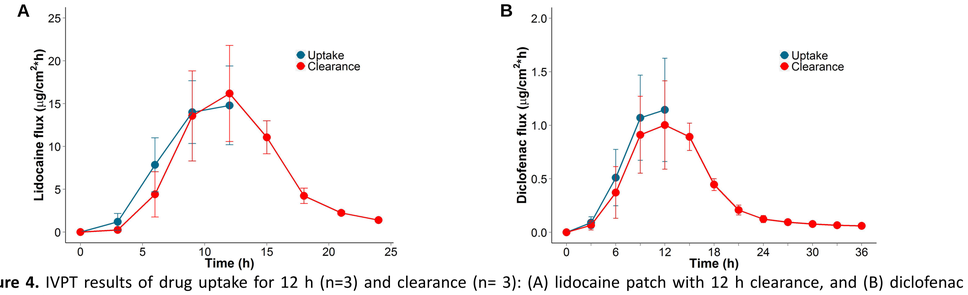

Figure 4. IVPT results of drug uptake for 12 h (n=3) and clearance (n= 3): (A) lidocaine patch with 12 h clearance, and (B) diclofenac patch with 24 h clearance.

Results

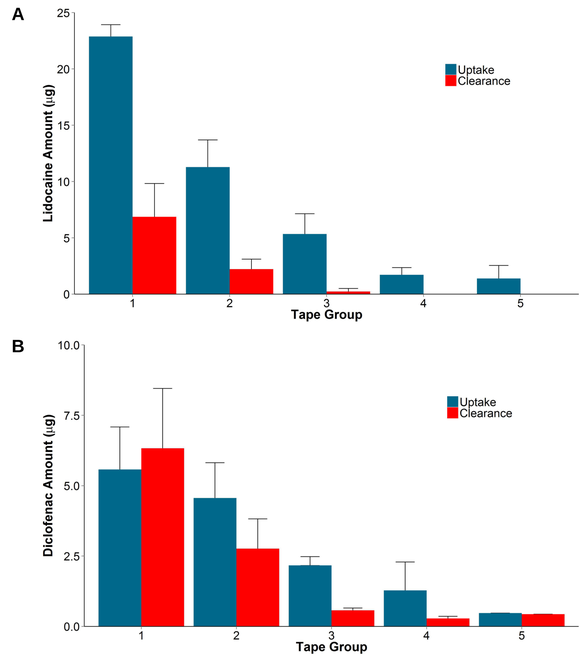

Figure 5. Amount of drug in tape strips groups at 12 h uptake (n=3) and clearance (n= 3): (A) lidocaine patch with 12 h clearance, and (B) diclofenac patch with 24 h clearance.

Conclusions

Comparisons of the rate of drug clearance from the SC along with the IVPT flux profile (Figure 4) over the clearance period may be meaningful. Information on the rate of drug delivery through the skin, which might be used in an assessment of bioavailability, may be meaningful from tape stripping measurements when clearance rates are large enough to provide a measurable decrease in SC drug concentration between uptake and clearance time points, as observed for lidocaine patch (Figure 1A and 5A). Although diclofenac does clear from the SC, its clearance rate is slow, possibly due to protein binding in the SC (Figure 1B and 5B). Amounts of diclofenac in the tape strips collected after clearance were not always smaller than in tape strips collected after uptake (Figure 1B). For drugs like diclofenac with slow skin clearance (Figure 3, 4B and 5B), estimates of drug clearance rates from tape stripping data may not be possible, although the amount of drug in the SC after uptake and clearance may have value in and of themselves when assessing comparative bioavailability. For these drugs, IVPT flux profiles may be useful for comparing the bioavailability between topical formulations. For drugs like lidocaine with quicker skin clearance (Figure 2, 4A and 5A), tape stripping measurements of the uptake and clearance amounts as well as the clearance rate may be useful assessments of comparative bioavailability, in addition to IVPT flux profiles.

Acknowledgment

Funding for this project was made possible, in part, by the Food and Drug Administration through grant 1U01FD004947. The views expressed in this poster do not reflect the official policies of the U.S. Food and Drug Administration or the U.S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.