In Vitro and In Vivo Evaluation of Two Lidocaine Topical Delivery Systems with or without the Influence of Transient Heat Exposure

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PURPOSE

Drug delivery from topical delivery systems (TDS) can be influenced by external factors such as temperature. The extent of such influences may depend on the formulation design and drug load of the respective TDS. The purpose of this study was to evaluate the effect of transient heat exposure on *1) in vitro* permeation of lidocaine across excised human skin and 2) *in vivo* bioavailability of lidocaine in healthy human volunteers, under harmonized study conditions, for two bioequivalent lidocaine TDS (Product A: Lidoderm® patch by Endo Pharmaceuticals and Product B: Lidocaine 5% patch by Mylan). A central consideration of the study design was to evaluate the influence of exposure to elevated heat early in the wear duration, before steady state is achieved, compared to exposure to elevated heat later in the wear duration, after steady state has been achieved for a TDS.

METHODS

In Vitro Studies

PermeGear® flow-through In-line diffusion system was used to perform IVPT experiments using two lidocaine TDS on five human skin donors; three different designs per donor: no heat exposure or 1.5 h heat exposure after either 4 h or 8.5 h of TDS application. The TDS was removed after 10 h for all designs, sampling continued until 15 h. *Ex vivo* human skin was dermatomed to a thickness of 297 ± 45 µm. The receiver solution was isotonic phosphate buffer with a flow rate of 1 (donor 1) or 2 rpm (donors 2-5). A circulating water bath was used to control the temperature of the diffusion cells at either 32 ± 2°C or 42 ± 2°C to mimic normal physiological skin temperature and elevated temperature conditions, respectively. Skin temperature was monitored using a traceable® infrared thermometer. All *in vitro* samples collected were analyzed using a validated HPLC method.

Table 1. Characteristics of lidocaine TDS used in the study

	Product A	Product B
Patch size (cm^2)	140	140
Drug Load (mg)	700	140
Appearance	White felt	Pigmented film
Weight (g)	15.57	3.5
Thickness (mm)	1.59	0.27
Adhesive	Water based	Non-water based

In Vivo Pharmacokinetic Studies

An open-label, six-way crossover pharmacokinetic (PK) study was conducted on healthy human subjects using two lidocaine TDS in presence and absence of transient heat. The PK profiles in the absence of heat application was characterized first (sessions 1 and 2) then heat was applied for four successive sessions (sessions 3 – 6). Heat was applied using a theratherm® heating pad for 1.5 h either 4 h or 8.5 h post patch application, with the target skin temperature of 42 ± 2°C. The skin temperature was monitored using Novatemp® skin sensors series 400. Blood samples were drawn at pre-determined time points throughout the duration of the study. Serum samples were analyzed to determine lidocaine concentrations using a validated LC-MS/MS method.

Approaches for IVIVC

Approach 1: R_{in} (µg/h) = J (µg/cm^2/h) x Area (cm^2)

R_{in} = CL x C_{ss}

CL = 0.64 L/min^1

Where, R_{in} = Rate of input, J = Flux, CL = Clearance, C_{ss} = Steady-state concentration

Approach 2: Predicted Concentration = (R_{input}/CL) * (1-e^{-kt})

k = 0.389 h^{-1}

Where, k= elimination rate constant, t= time

Approach 3: Deconvolution of patch PK profile by Unit Impulse Response based approach using Phoenix WinNonlin®.

Parameter estimates obtained from existing intravenous data used[2]:

A = 4698.51 ng/mL, Alpha = 9.6 h^{-1}, B = 1303.71 ng/mL, Beta = 0.54 h^{-1}

Polynomial equations describing the correlation between Fraction absorbed versus Fraction permeated in the absence of heat for the two TDS :

Product A: y=29.849x^2 + 0.5417x - 0.0002

Product B: y=5.5305x^2 + 0.0577x - 0.001

Where, y: Observed fraction absorbed *in vitro*

x: Predicted fraction absorbed *in vivo*

Predicted concentrations in the heat arms included an *in vitro* heat factor calculated by dividing the flux values in heat arm with the flux in baseline arm.

[1]Lidoderm(R) [package insert]. Endo Pharmaceuticals, C. F., PA; September 2004.

[2]Kondamudi et al. Lidocaine Transdermal Patch: Pharmacokinetic Modeling and In Vitro – In Vivo Correlation (IVIVC) . AAPS PharmSciTech 2015,17(3):588-96.

RESULTS

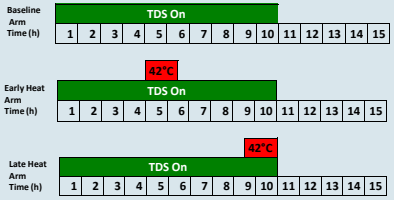

Figure 1. Schematic representation of the harmonized study design for both *in vitro* and *in vivo* PK studies

In Vitro Studies

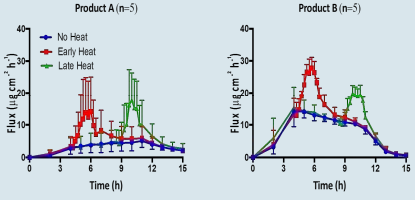

Figure 2. Flux profiles of the two lidocaine TDS with either early, late, or no heat exposure. (Mean ± SD from 5 skin donors with n=4 replicates per donor)

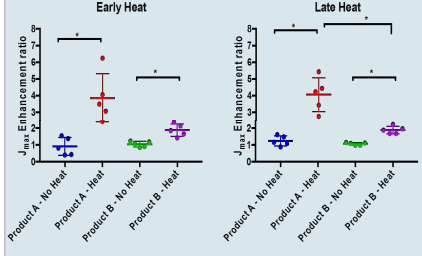

Figure 3. Heat effect determined by the flux enhancement ratios, at Jmax for Early and Late Heat designs, respectively. Enhanced flux values were compared to values obtained from the No Heat study designs. No significant differences ($p > 0.05$) were found between the two lidocaine TDS for Early Heat but significant difference was seen for Late Heat effect. (Mean ± SD from 5 skin donors with n=4 replicates per donor)

In Vivo Pharmacokinetic Studies

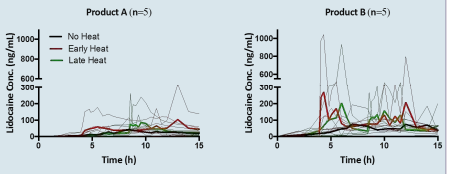

Figure 4. Serum lidocaine concentrations obtained from 5 volunteers after applying the two TDS with 1.5 h of either early or late heat exposure.

Approaches for IVIVC

Table 2. Approach 1 for IVIVC: Estimation of steady-state concentration (C_{ss}) *in vivo*.

	Observed C_{ss} *In vivo* (ng/mL)	Estimated C_{ss} *In vitro* (ng/mL)	*p*-value (unpaired t-test)
Product A	26.86 ± 34.69	16.63 ± 9.26	0.5419
Product B	45.80 ± 39.56	37.43 ± 2.57	0.6495

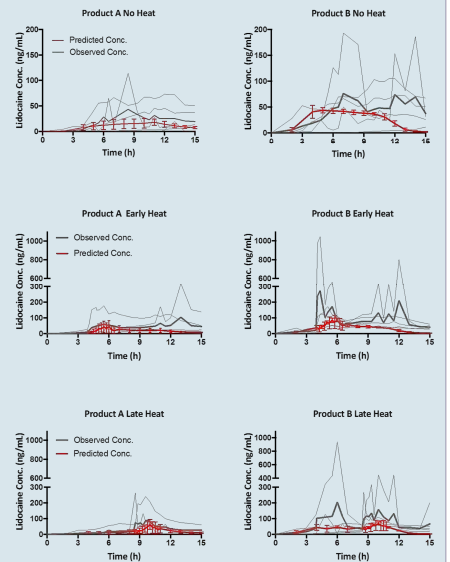

Figure 5. Approach 2 for IVIVC: Observed and predicted lidocaine concentrations for the two lidocaine TDS.

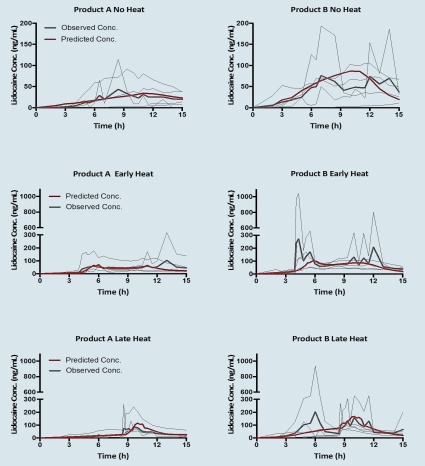

Figure 6. Approach 3 for IVIVC: Mean observed and predicted lidocaine concentrations for the two lidocaine TDS.

CONCLUSIONS

- Both lidocaine TDS exhibited a significant heat effect *in vitro* (Figure 2)
- *In vitro* Product A shows increased variability in flux values during the period of heat application compared to Product B (Figure 1). It is hypothesized that the differences could be attributed to the differences in the structure of the two different systems evaluated where product A is a hydrogel based system and product B is a adhesive matrix based system.
- *In vivo* mean PK profiles for the TDS obtained from five volunteers showed increased drug levels during heat application. Higher variability is observed with Product B compared to Product A. The PK dataset is incomplete since the study is currently underway. We will have better estimates when we have the complete dataset which includes 12 subjects.
- Approach 1 was able to adequately predict *in vivo* Css using *in vitro* data for this limited dataset.
- Point-to-point prediction of the entire PK profile was successfully made for all study arms using the limited data set (Figures 5 and 6).

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