Title	*In Vitro - In Vivo* Correlation for Two Bioequivalent Lidocaine Patches under Transient Heat Exposure
Keywords	drug permeation, bioavailability, temperature, lidocaine
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Abstract	The purpose of our study was to evaluate the effect of transient heat exposure on *in vitro* permeation of lidocaine in excised human skin and *in vivo* bioavailability in healthy human volunteers under harmonized study conditions. A central consideration in the study design was to evaluate the influence of exposure to elevated heat early in the wear duration before steady-state is achieved compared with exposure to elevated heat later in the wear duration after steady-state has been achieved. An open-label, six-way crossover pharmacokinetic study was conducted on healthy human subjects. Skin temperature of 42 ± 2°C was achieved by application of a heating pad over the patches. Early heat was applied for 90 mins, 4 hours post-patch application and late heat was applied for 90 mins, 8.5 hours after application. Pharmacokinetic profile in the absence of heat application was obtained. Similar study design was used for *in vitro* permeation tests (IVPT) performed using *ex vivo* human skin to investigate dermal absorption from two patches. A circulating water bath was used to mimic heat exposure. A 2.0 – 4.5 fold and a 1.8 – 4.3 fold enhancement in J_{max} was observed with early and late heat application. A 5.0 – 6.2 fold and a 2.3 – 2.5 fold enhancement in C_{max} was observed with early and late heat application respectively. The observed *in vivo* concentrations were de-convoluted to obtain the fraction of drug absorbed. The correlation between fraction absorbed *in vivo* and fraction permeated *in vitro* for the baseline study arm was described by a polynomial equation. Heat factor was incorporated into the equation to predict the heat-induced enhancement in lidocaine bioavailability. IVPT studies performed under the same conditions as those of interest *in vivo* may have the potential to correlate with and be predictive of *in vivo* results, and may have the utility to evaluate heat effects *in vitro*.