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# *In Vitro* Evaluation of a Buprenorphine Transdermal Delivery System with Transient Heat Exposure and the Correlation of *In Vitro* Results with Existing *In Vivo* Results

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## PURPOSE

Heat sources such as heating pads, electric blankets and saunas can potentially alter the drug delivery profile from formulations applied to the skin. Buprenorphine is an opioid indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Exposure of a buprenorphine transdermal delivery system (TDS) to a heating pad or to other external heat sources may lead to an increase in the bioavailability of buprenorphine that could result in a possible overdose and death, according to the product labeling for buprenorphine TDS (BUTRANS®). Similar considerations relating to heat exposure may apply to other TDS products, and it would be of considerable value to be able to evaluate such heat effects *in vitro*. The purpose of this study was to investigate the effect of heat on buprenorphine delivery (skin permeation) *in vitro* by using buprenorphine TDS (BUTRANS®) and to evaluate the ability of *in vitro* permeation tests (IVPT) to correlate with and be predictive of the potential heat-enhanced drug delivery *in vivo*.

## METHODS

***Study Design***

IVPT studies were performed using PermeGear In-Line flow-through diffusion cells. The *in vitro* study design was harmonized to match that of the *in vivo* heat effect study described in the Clinical Pharmacology and Biopharmaceutics Review document for BUTRANS® available at Drugs@FDA. Human skin from four donors with four replicates per donor was used for each study arm; one performed at normal skin surface temperature, and the other performed with periods of transient elevated heat exposure. The heat arm had heat application early in the experiments from 24 h to 31 h and later in the experiments from 72 h to 79 h. Heat was applied for three 2 h intervals over each 7 h period (with 30 minute intervals between heat application). For both the baseline and heat arm, the TDS was removed at 168 h and sampling was continued until 174 h. A 0.97 $cm^2$ circular disc of the buprenorphine TDS was applied upon the skin within the permeation area of the diffusion cell. Skin temperature was maintained at either 32 ± 2˚C or 42 ± 2˚C, representing normal and elevated skin temperature conditions, respectively. Brij® 98 (Oleth-20) at 0.1% was added to the receptor solution to ensure sufficient solubility of buprenorphine in an aqueous media. Receptor solution was collected at pre-determined time intervals and analyzed using a validated high performance liquid chromatography (HPLC) method.

***Data Analysis and in vivo-in vitro correlation (IVIVC)***

Student's t-test was used to compare the differences in the means of flux and cumulative amount; significant differences were declared at $p \leq 0.05$. Fraction permeated (Fp) was calculated from the *in vitro* studies. Phoenix WinNonlin® was used to perform numerical deconvolution to obtain the fraction of drug absorbed (Fa) and convolution to obtain predicted concentrations. Unit impulse response (UIR) values were obtained by fitting IV bolus data obtained from literature (*Huestis et al. Intravenous Buprenorphine and Norbuprenorphine Pharmacokinetics in Humans, Drug and Alcohol Dependence, Volume 131, Issue 3, 2013, Pages 258-262)* to a two-compartment PK model. The correlation between Fa *in vivo* and Fp *in vitro* for the baseline study arm was described by a polynomial equation $40.947x^2+1.3685x+0.002$. Two heat factor terms (Hv is heat factor obtained from *in vivo* data and Hr is heat factor obtained from *in vitro* data) were introduced into the calculations to obtain predicted concentration following application of transient heat. The following relationships were used:

Fp = Cumulative amount permeated at time t/Dose

Hv = Mean heat arm concentration value/Mean baseline arm concentration value

Hr = Mean heat arm flux value/Mean baseline arm flux value

Predicted heat arm concentration = Predicted baseline arm concentration × (Hv or Hr)

## RESULT(S)

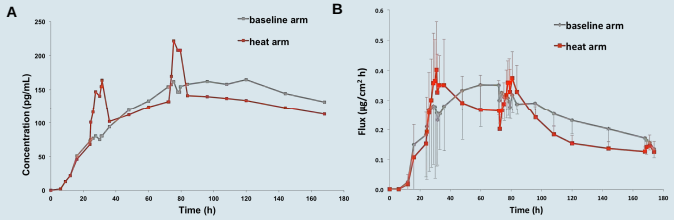


**Figure 1. (A)** *In vivo* concentration versus time profile obtained from the *Clinical Pharmacology and Biopharmaceutics Review* document for BUTRANS® available at Drugs@FDA (n=20). **(B)** Flux profile for BUTRANS® (mean ± SD) (n=4 human skin (HS) donor, 4 replicates/donor) from IVPT data

**Table 1.** Heat-induced enhancement in maximum flux (Jmax) in vitro and maximum concentration (Cmax) in vivo (mean ± SD, n=4 human skin (HS) donor for in vitro and n=20 for subjects in vivo )

| | | | | | |
|---|---|---|---|---|---|
| | (at 31 h) | (after baseline correction with J at 24h→ 1.13 ± 0.17) | (after baseline correction with J at 24h→ 2.02± 0.70) | baseline corrected values→ **1.57**) | |
| | **late heat** (at 79 h) | 0.38 ± 0.05 | 0.46 ± 0.02 | **1.21** | 0.1922 |
| **HS-3** | **early heat** (at 33 h) | 0.16 ± 0.04 | 0.32 ± 0.10 | **2.00** | 0.0215 |
| # | **late heat** (at 81 h) (at 31 h) | 0.26 ± 0.00 (after baseline correction with J at 24h→ 1.13 ± 0.17) | 0.31 ± 0.01 (after baseline correction with J at 24h→ 2.02± 0.70) | **1.19** baseline corrected values→ **1.57**) | 0.3242 |
| | **late heat** (at 79 h) | 0.38 ± 0.05 | 0.46 ± 0.02 | **1.21** | 0.1922 |
| **HS-3** | **early heat** (at 33 h) | 0.16 ± 0.04 | 0.32 ± 0.10 | **2.00** | 0.0215 |
| | **late heat** (at 81 h) | 0.26 ± 0.00 | 0.31 ± 0.01 | **1.19** | 0.3242 |
| **HS-4** | **early heat** (at 33 h) | 0.24 ± 0.01 | 0.43 ± 0.03 | **1.79** | 0.0024 |
| | **late heat** (at 81 h) | 0.33 ± 0.01 | 0.44 ± 0.03 | **1.33** | 0.0206 |
| **In vivo** | **early heat** (at 31.5 h) | 80.5 ± 26.83 | 164 ± 39.23 | **2.04 (±0.83)*** | - |
| | **late heat** (at 75.5 h) | 161.5 ± 42.49 | 221.5 ± 80.64 | **1.37 (±0.61)*** | - |

#Baseline correction was applied to HS-2 to normalize the initial dissimilarity in flux profiles arising due to high variability seen among replicates in the baseline and heat arm.

*(±z) Represents the uncertainty associated with the ratio y/x which is given by the following equation, where δ = SD $z = \sqrt{\left(\frac{\partial y}{y}\right)^2 + \left(\frac{\partial x}{x}\right)^2}$

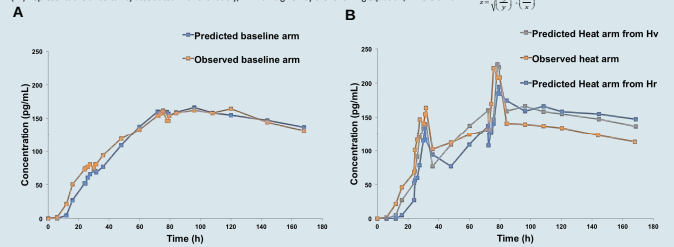


**Figure 2.** Plot for observed and predicted *in vivo* concentration versus time profiles for baseline arm (**A**) and heat arm (**B**).

**Table 2.** Predicted vs. observed pharmacokinetic parameters (Cmax and $AUC_{0\text{-}168h}$) as well as percent prediction error (%PE) for baseline arm and heat arm

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Observed** | 20848.88 | 19598.00 | 19598.00 | 164.50 | 164.00 | 221.50 | 164.00 | 221.50 |
| **Predicted** | 20282.81 | 20086.99 | 20979.13 | 166.31 | 133.88 | 194.27 | 139.78 | 227.07 |
| **% PE** | 2.72 | -2.50 | -7.05 | -1.1 | 18.37 | 12.29 | 14.77 | -2.51 |
| **Observed** | 20848.88 | 19598.00 | 19598.00 | 164.50 | 164.00 | 221.50 | 164.00 | 221.50 |
| **Predicted** | 20282.81 | 20086.99 | 20979.13 | 166.31 | 133.88 | 194.27 | 139.78 | 227.07 |
| **% PE** | 2.72 | -2.50 | -7.05 | -1.1 | 18.37 | 12.29 | 14.77 | -2.51 |

## CONCLUSIONS

- When exposed to an elevated temperature *in vitro*, under conditions that closely matched *in vivo* study conditions, buprenorphine TDS (BUTRANS®) exhibited an increase in the rate and extent of drug delivery relative to its baseline drug delivery at normal (32 ± 2˚C) skin temperature conditions.
- The elevated rate of buprenorphine delivery through the skin did not return to baseline levels until several hours after the external heat source was removed.
- The ratio of heat-induced enhancement over baseline observed for $J_{max}$ in our *in vitro* studies was reasonably consistent with the corresponding enhancement in $C_{max}$ reported in the *in vivo* study.
- Accounting for variability between the *in vitro* and *in vivo* study populations, the *in vivo* plasma pharmacokinetic profile of buprenorphine predicted based upon our IVPT study results compares well with the observed results *in vivo*.
- Our results indicate that an *in vitro - in vivo* correlation (IVIVC) can be established for buprenorphine TDS, both, under normal temperature conditions and when the TDS is exposed to an elevated temperature.
- The results also suggest that 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 TDS heat effects *in vitro*.

## ACKNOWLEDGEMENTS

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