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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INTRODUCTION

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 used for the treatment of moderate acute and chronic pain. 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 label 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 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 for which results are published in the buprenorphine TDS (Butrans®) product label. Human skin from three donors with four replicates per donor was used for each study arm; one performed at normal skin surface temperature, and the other 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. For both the baseline and heat arm, the transdermal system 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 to mimic normal and elevated skin temperature conditions, respectively. Brij® 98 at 0.1% was added to the receptor solution to ensure sufficient solubility of buprenorphine in an aqueous media. Receptor solution was collected at predetermined time intervals and analyzed using a validated high performance liquid chromatography (HPLC) method. *In vivo* study design and data was obtained from the *Clinical Pharmacology and Biopharmaceutics Review* document for Butrans® available at Drugs@FDA.

HPLC method

A HPLC method was developed to elute the drug followed by the surfactant in each sample injection to ensure no interference from the surfactant with the subsequent injections.

Data Analysis and IVIVC

Student's t-test was used for comparing the differences in the means of flux and cumulative amount and significant differences were declared at $p \leq 0.05$. Fraction permeated (Fp) was calculated from the *in vitro* studies. The observed *in vivo* concentrations were deconvoluted to obtain the fraction of drug absorbed (Fa). The correlation between fraction absorbed *in vivo* and fraction permeated *in vitro* for the baseline study arm was described by a polynomial equation. This equation was then used to obtain predicted concentrations for baseline arm. 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/Total amount of drug permeated *in vitro*

Fa = $(AUC_{0\text{-}t} * CL)/F*D$

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

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

A

	Patch On																		
Time (h)	1	24	25	26	27	28	29	30	31	32	71	72	73	74	75	76	77	78	79	168	174

B

			42°C		42°C		42°C				42°C			42°C							
	Patch On																				
Time (h)	1	24	25	26	27	28	29	30	31	32	71	72	73	74	75	76	77	78	79	168	174

Figure 1. Study design for baseline arm **(A)** and heat arm **(B)**.

RESULTS

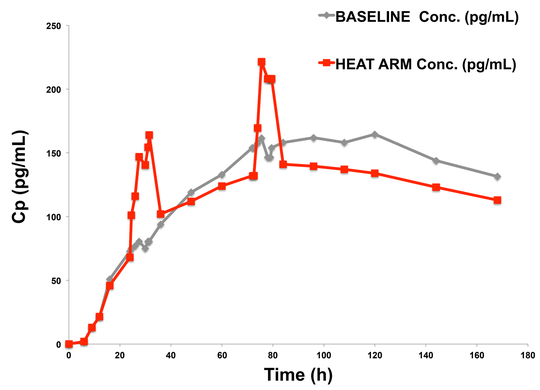

Figure 2. *In vivo* concentration versus time profile obtained from the *Clinical Pharmacology and Biopharmaceutics Review* document for Butrans® available at Drugs@FDA.

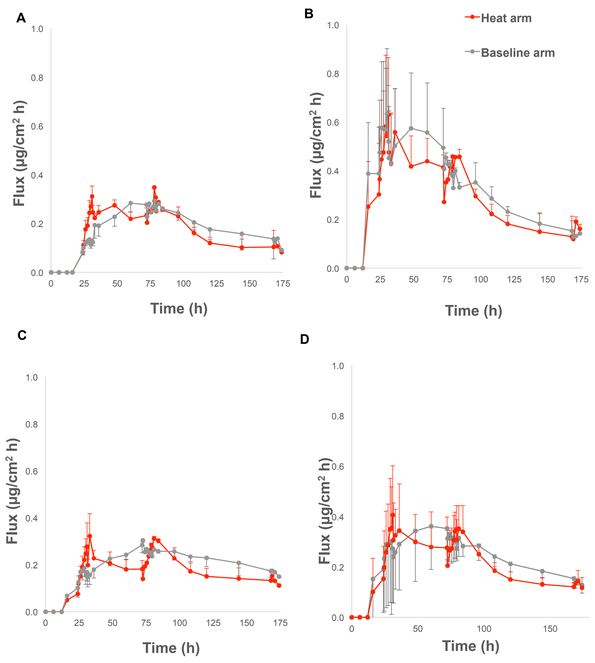

Figure 3. Flux profile for Butrans® from human skin donor 1 **(A),** 2 **(B),** 3 **(C)** and mean of three donors **(D)**. (mean ± SD) (n=3 human skin donor, 4 replicates/donor)

Table 1. Heat-induced enhancement in Jmax and Cmax

		Jmax or Cmax (µg/cm² h or pg/mL)	Baseline Arm (x)	Heat Arm (y)	*Enhancement ratio (y/x)*	*#p value*
HS-1	**early heat** (at 31 h)	0.14 ± 0.01	0.31 ± 0.02	**2.21**	0.0003
	late heat (at 78 h)	0.29 ± 0.02	0.37 ± 0.03	**1.27**	0.0572
HS-2	**early heat** (at 31 h)	0.52 ± 0.39 (after baseline correction with J at 24 h→ 1.13 ± 0.17)	0.63 ± 0.30 (after baseline correction with J at 24 h→ 2.02 ± 0.70)	(ratio obtained using baseline corrected values→ **1.57**)	0.0483
	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
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)***	-

#p values were obtained from unpaired t test

Table 2. Heat factor obtained from *in vitro* (Hr) and *in vivo* (Hv) heat arms

Time (h)	Hv	Hr
24.0	0.93	0.92
24.5	1.35	1.02
26.0	1.51	1.12
27.5	1.83	1.22
30.0	1.87	1.70
31.0	1.92	1.88
31.5	2.04	1.58
36.0	1.09	1.33
72.0	0.86	0.77
72.5	0.86	0.67
74.0	1.08	0.81
75.5	1.37	0.88
78.0	1.42	1.11
79.0	1.42	1.16
79.5	1.35	1.12
84.0	0.89	1.18

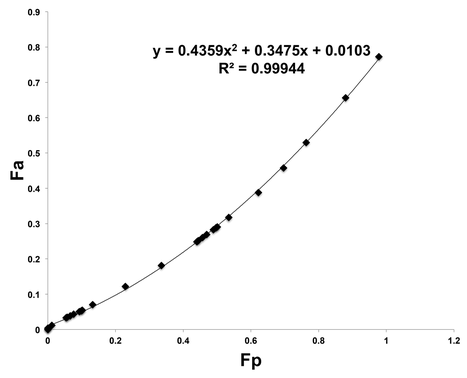

Figure 4. Level A correlation plot for Fa versus Fp.

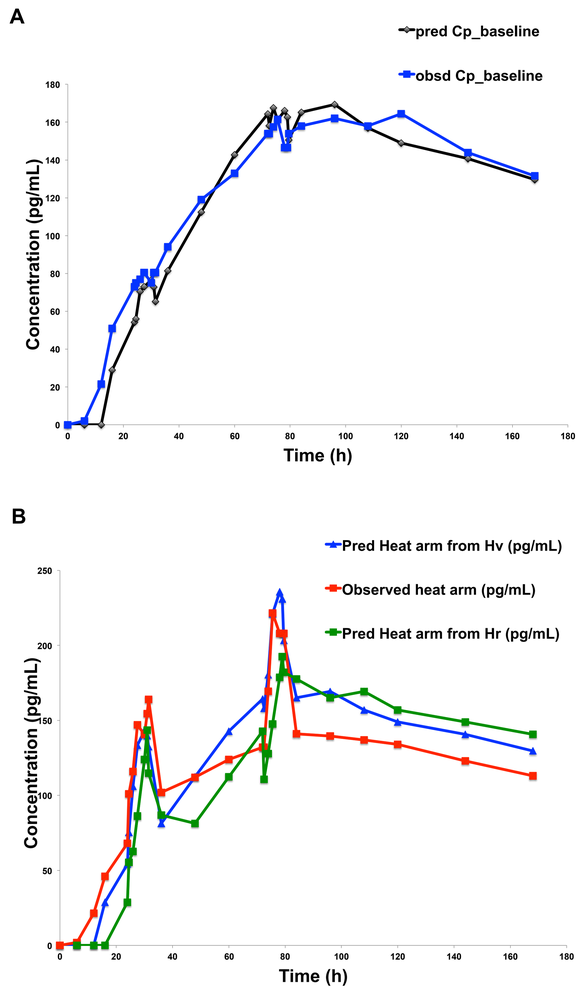

Figure 5. Plot for observed and predicted concentration versus time profiles for baseline arm (**A**) and heat arm (**B**).

Table 3. Predicted vs. observed pharmacokinetic parameters (Cmax and $AUC_{0\text{-}168h}$) as well as percent prediction error (%PE) for the baseline arm

	Predicted	Observed	%PE
Cmax (pg/mL)	169.33	164.50	-2.94
$AUC_{0\text{-}168h}$ (pg*h/mL)	20930.36	21088.25	0.75

Table 4. Predicted vs. observed pharmacokinetic parameters (Cmax – early heat, Cmax – late heat, and $AUC_{0\text{-}168h}$) as well as percent prediction error (%PE) for heat arm using Hv

	Predicted	Observed	%PE
Cmax-early heat (pg/mL)	143.28	164.00	12.63
Cmax-late heat (pg/mL)	235.67	221.50	-6.40
$AUC_{0\text{-}168h}$ (pg*h/mL)	18337.09	16773.75	-9.32

Table 5. Predicted vs. observed pharmacokinetic parameters (Cmax – early heat, Cmax – late heat, and $AUC_{0\text{-}168h}$) as well as percent prediction error (%PE) for heat arm using Hr

	Predicted	Observed	%PE
Cmax-early heat (pg/mL)	143.49	164.00	12.51
Cmax-late heat (pg/mL)	192.63	221.50	13.03
$AUC_{0\text{-}168h}$ (pg*h/mL)	17309.23	16773.75	-3.19

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 (ambient and 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 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.
- 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*.

ACKNOWLEDGEMENT

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