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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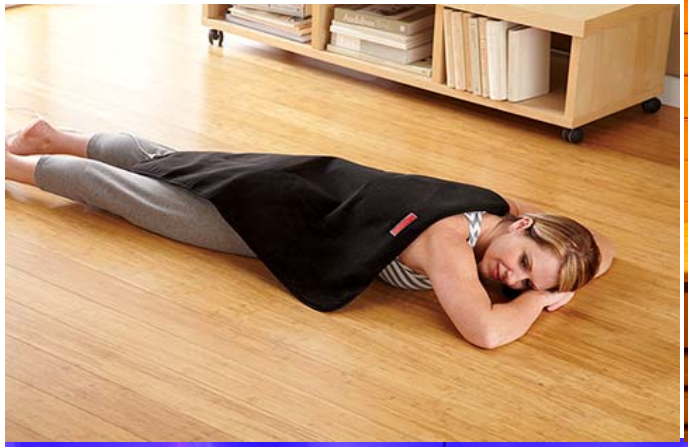
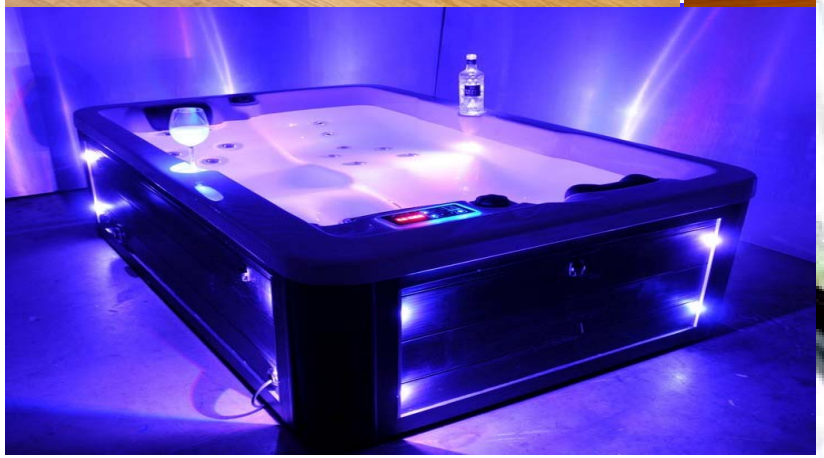
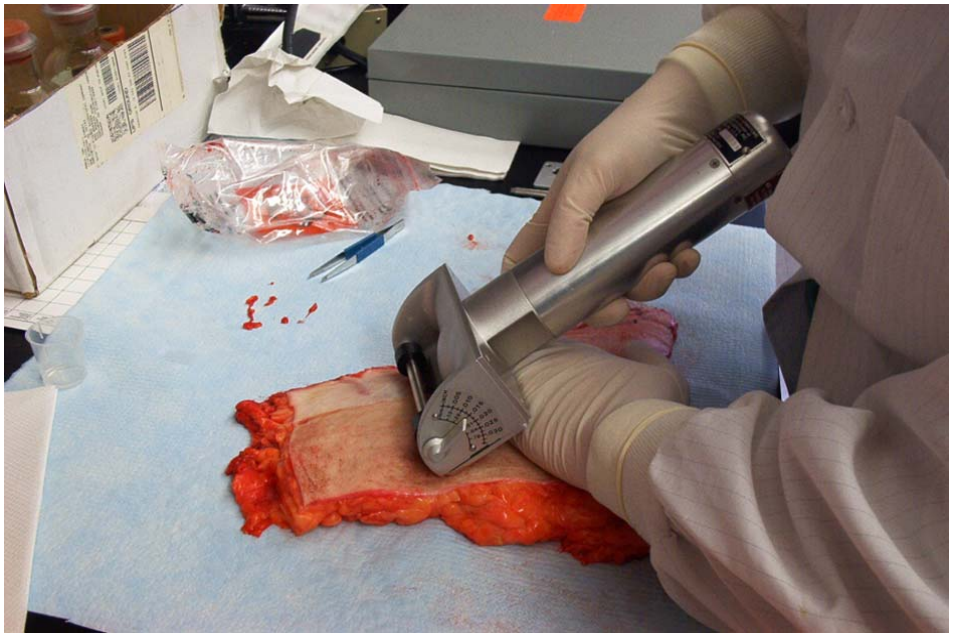


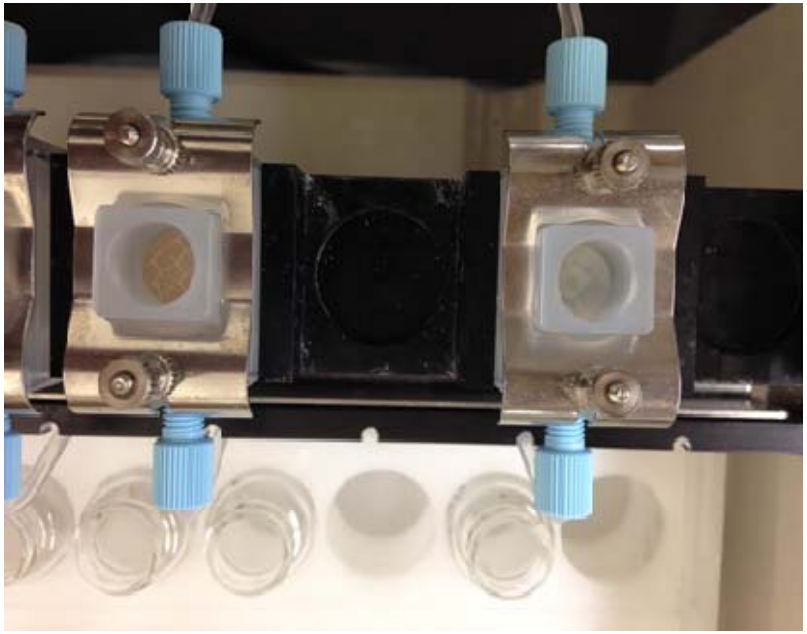


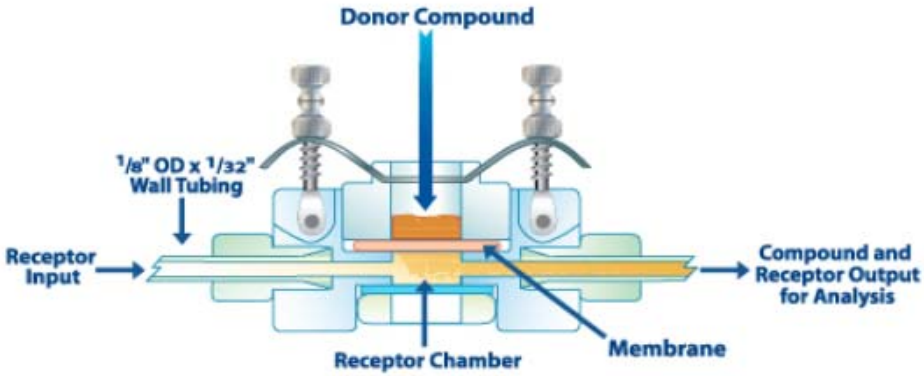
Possible Effects of Elevated Temperature

1. Drug release from formulation
2. Barrier properties of Stratum Corneum
3. Diffusion of solute through skin
4. Rate of dermal clearance

In Vitro Permeation Test (IVPT)







In-Line Diffusion Cell

Study design

Baseline Study Arm

	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

Heat Study Arm

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

In vivo data

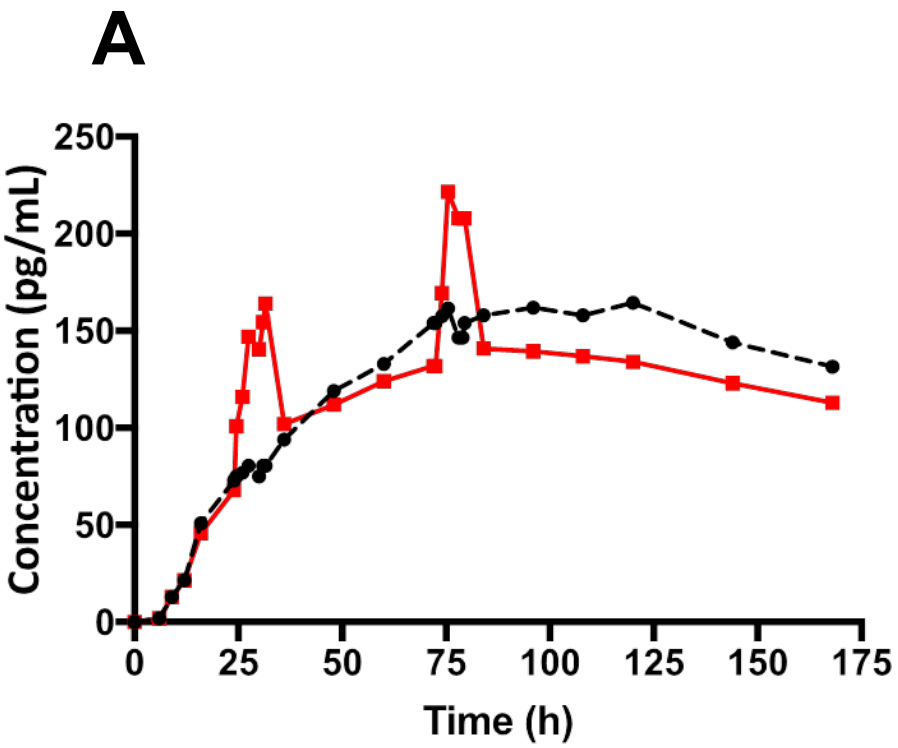


Figure 1. (A) *In vivo* concentration versus time profile obtained from the *Clinical Pharmacology and Biopharmaceutics Review* document for BUTRANS® available at Drugs@FDA (n=20).

In vivo data

In vitro data

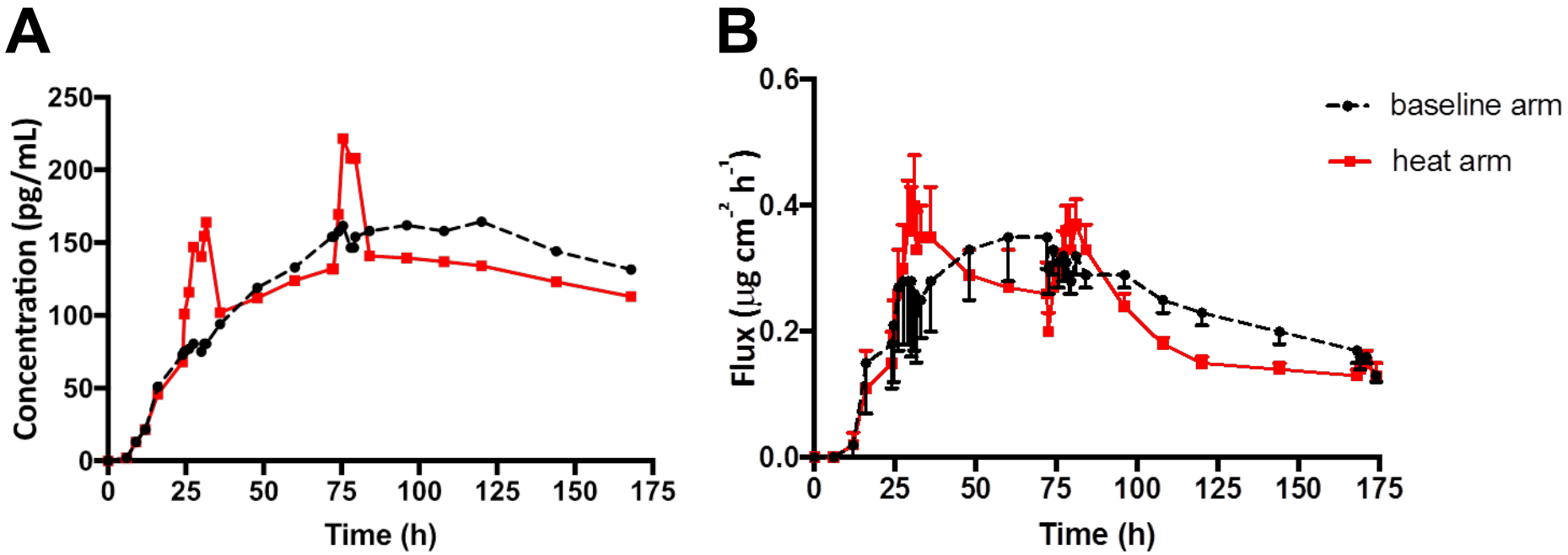
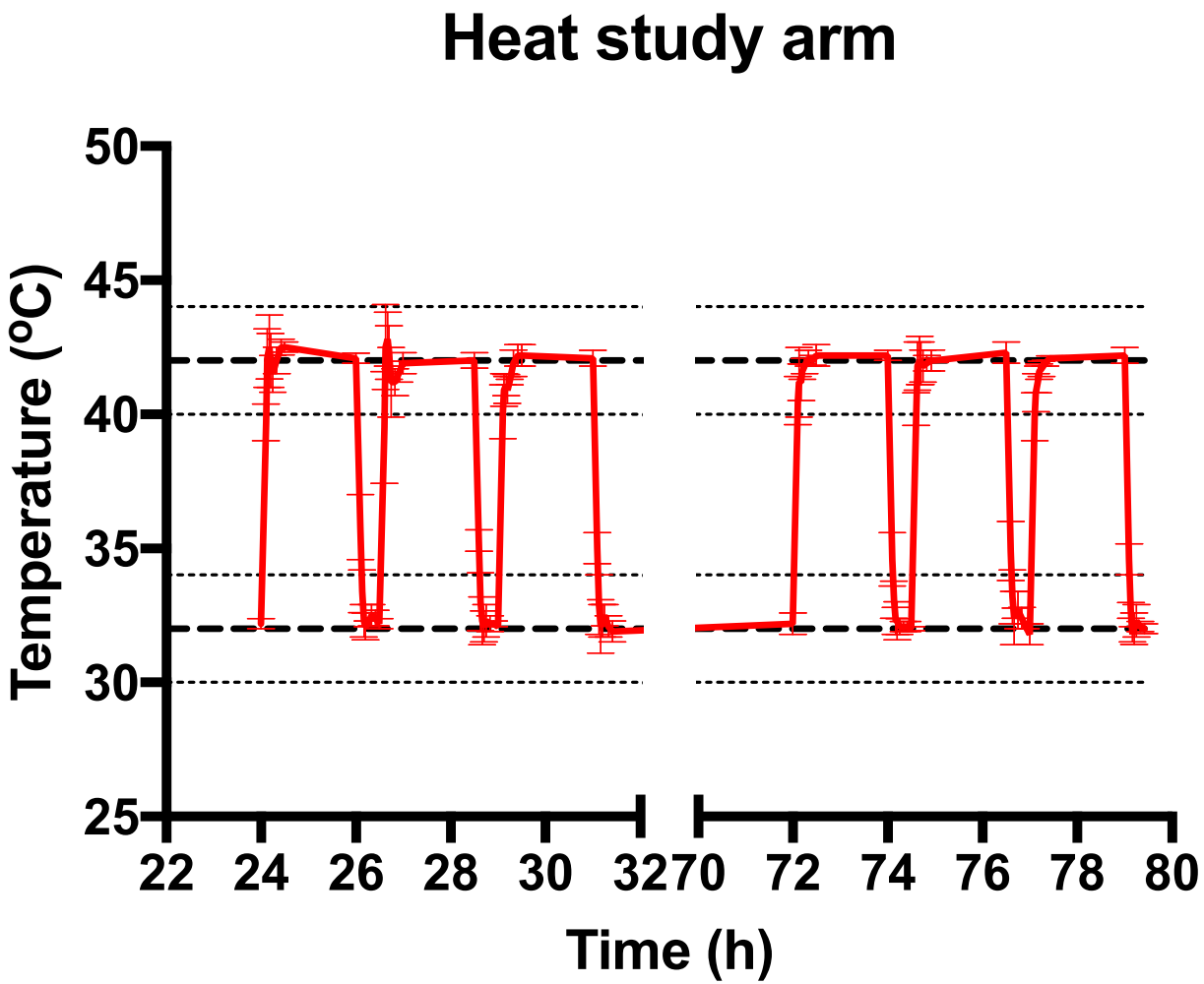


Figure 1. (A) *In vivo* concentration versus time profile obtained from the *Clinical Pharmacology and Biopharmaceutics Review* document for BUTRANS® available at Drugs@FDA (n=20). (B) Flux profile for BUTRANS® (mean ± SD) (n=4 human skin (HS) donor, 4 replicates/donor) from IVPT data

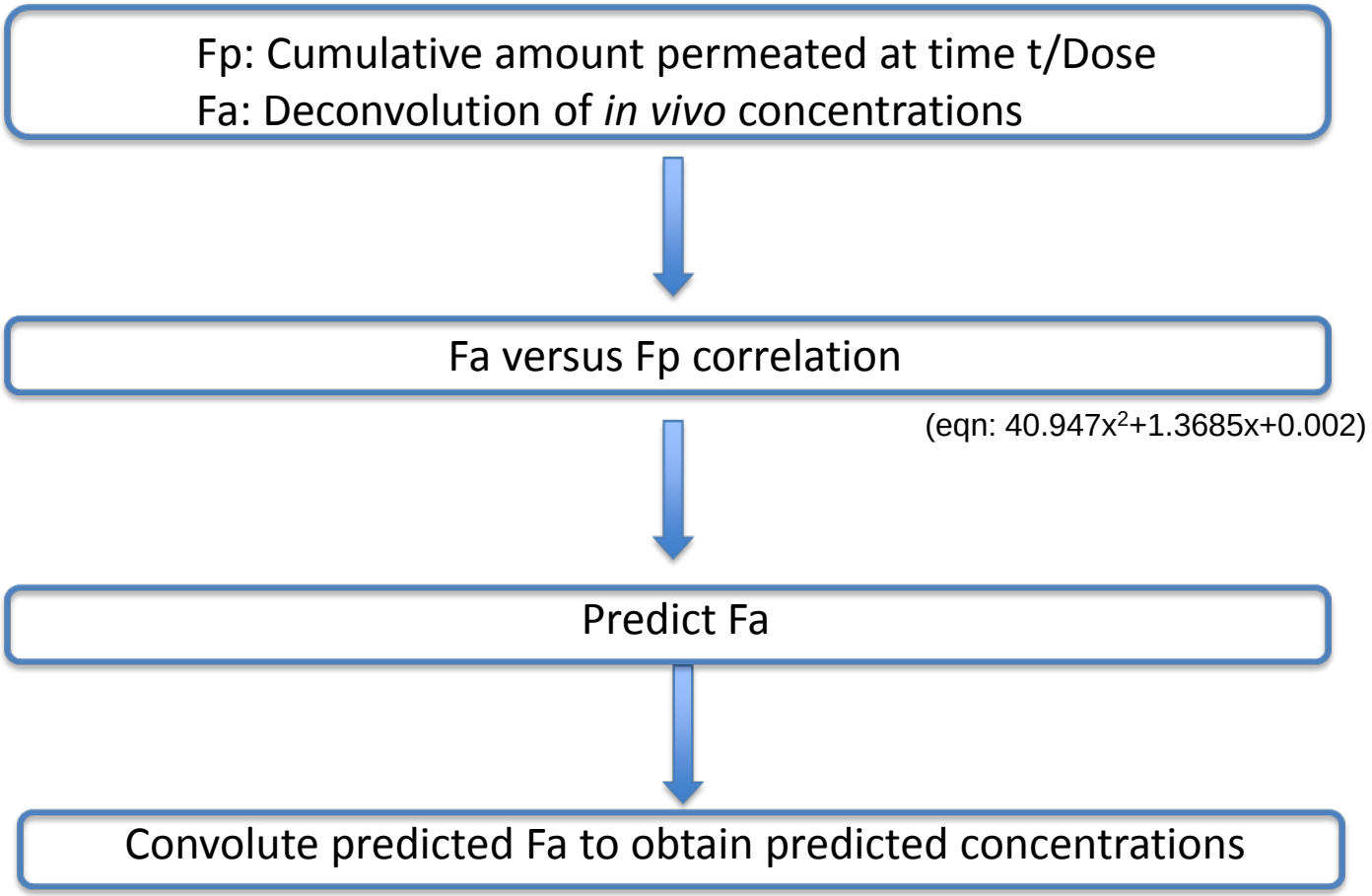
Skin Temperature versus Time



Heat induced enhancement

	Jmax or Cmax (µg/cm² h or pg/mL)	Baseline Arm (x)	Heat Arm (y)	*Enhancement ratio (y/x)*	#*p value*
In vitro					
Mean (n=4)	**early heat**	0.18 ± 0.05	0.35 ± 0.07	**1.89 (±0.28)**	0.0026
	late heat	0.32 ± 0.05	0.40 ± 0.07	**1.25 (±0.06)**	0.0073
In vivo					
Mean (n=20)	**early heat**	80.5 ± 26.83	164 ± 39.23	**2.04 (±0.83)**	-
	late heat	161.5 ± 42.49	221.5 ± 80.64	**1.37 (±0.61)**	-

Prediction of Concentration versus Time profile



Observed versus Predicted Profile

Baseline Arm

A

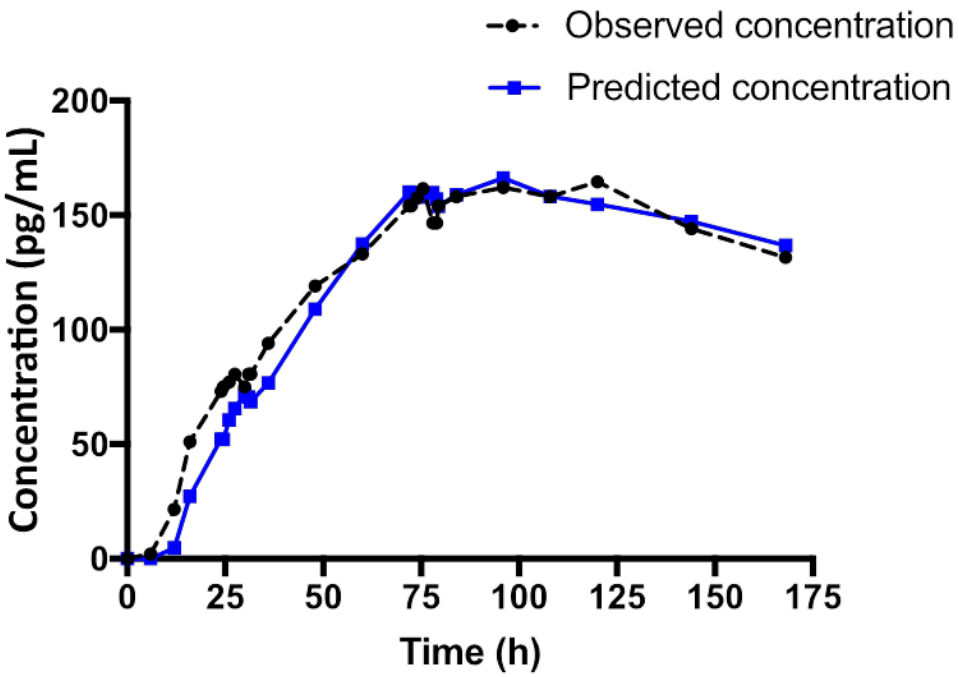


Figure 2. Plot for observed and predicted *in vivo* concentration versus time profiles for baseline arm (A)

Observed versus Predicted Profiles

Baseline Arm

Heat Arm

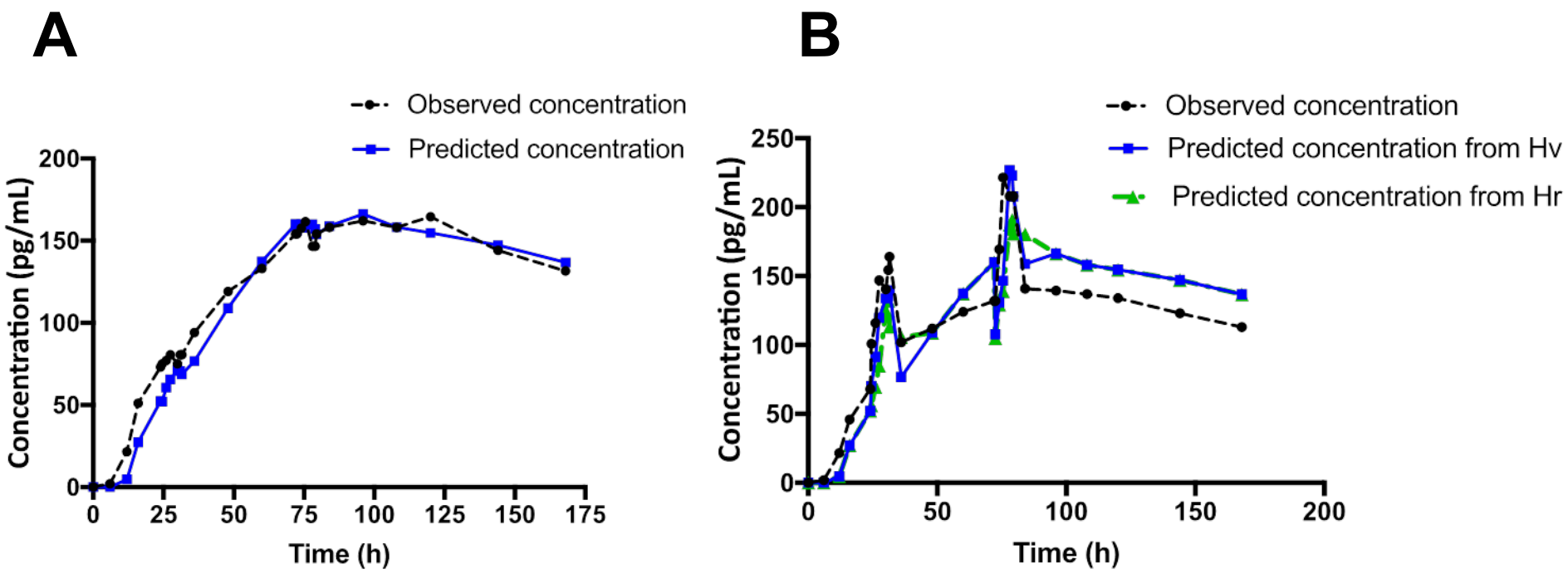


Figure 2. Plot for observed and predicted *in vivo* concentration versus time profiles for baseline arm (A) and heat arm (B).

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)

% Prediction Error

	AUC_{0-t} (pg*h/mL)			Cmax (pg/mL)				
	Baseline Arm	**Heat Arm (Hr)**	**Heat Arm (Hv)**	**Baseline Arm**	**Early Heat (Hr)**	**Late Heat (Hr)**	**Early Heat (Hv)**	**Late Heat (Hv)**
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	19.36	13.83	14.77	-2.51

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

CONCLUSIONS

- *In vitro*, an increase in the rate and extent of drug delivery relative to its baseline

- The elevated rate of buprenorphine delivery through the skin did not immediately return to baseline after the external heat source was removed.

- The ratio of heat-induced enhancement for J_{max} in our *in vitro* studies was reasonably consistent with the corresponding enhancement in C_{max} reported in the *in vivo* study.

- 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*.

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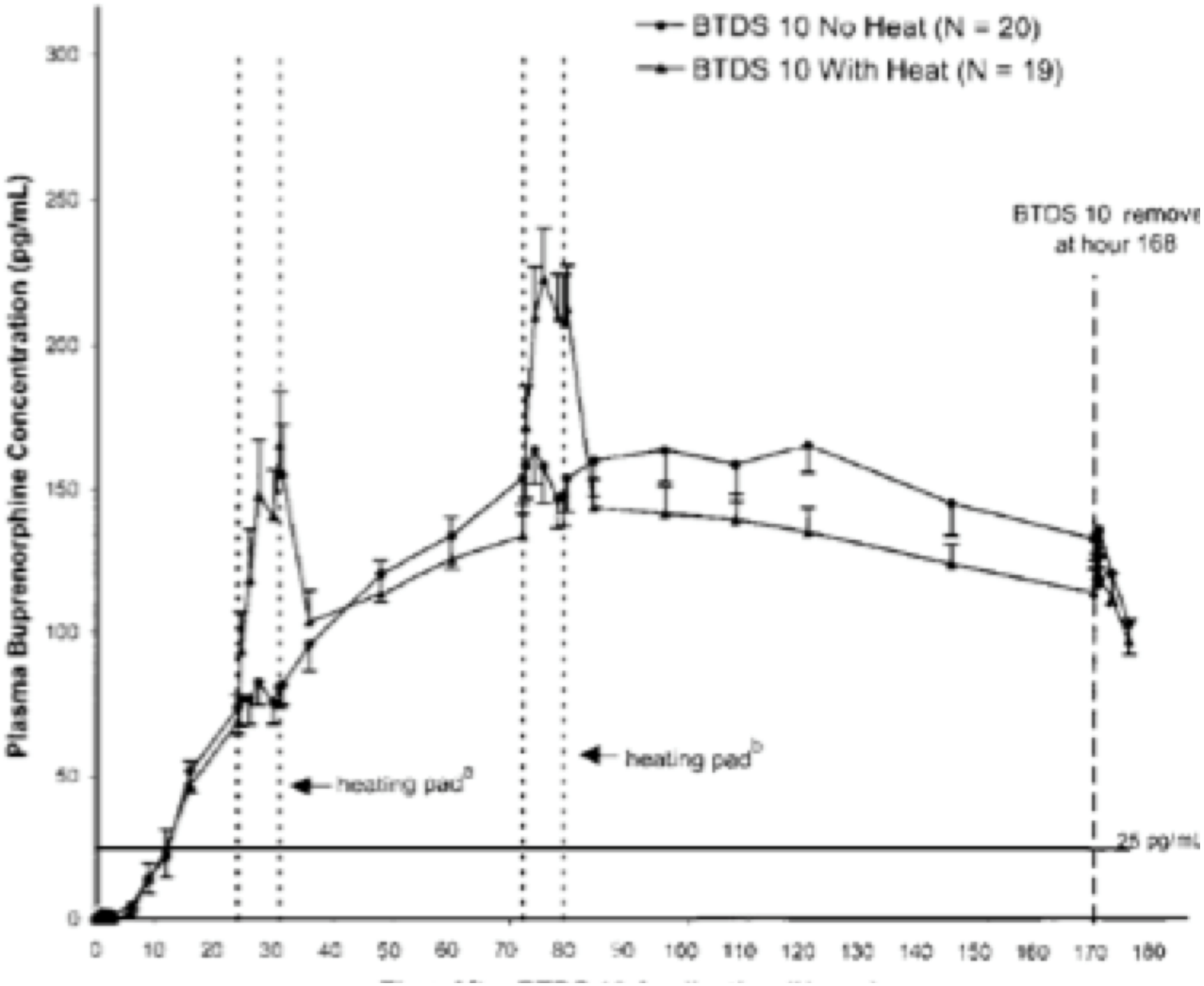
Heat induced enhancement

	Jmax or Cmax (μg/cm² h or pg/mL)	Baseline Arm (x)	Heat Arm (y)	*Enhancement ratio (y/x)*	#*p value*
In vitro					
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 24h→ 1.13 ± 0.17)	0.63 ± 0.30 (after baseline correction with J at 24h→ 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
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
Mean	**early heat (exclude HS-2)**	0.18 ± 0.05	0.35 ± 0.07	**1.94 (1.89)**	0.0026
	late heat	0.32 ± 0.05	0.40 ± 0.07	**1.25**	0.0073
In vivo					
Mean	**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)**	-


BTDS 10 No Heat (N = 20)
BTDS 10 With Heat (N = 19)
Plasma Buprenorphine Concentration (pg/mL)
BTDS 10 remove
at hour 168
heating pad
heating pad
25 pg/mL
0
50
100
150
200
250
300
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180