

JNIVERSITY SCHOOL OF PHARMACY

אוו ווו עונו	An in vitro model that exhibits IVIVC is a powerful tool in									
biopharmaceutical drug development because it can efficiently predict										
drug produ	drug product performance in vivo. While the concept of IVIVC has									
been utilize	ed most o	ften for d	oral dosa	ge forms, demonstrations of						
The present	IN VITRO MC t investigat	ion used i	n for othe multiple a	r dosage forms are emerging.						
A IVIVC for	Transderm	al Delivery	v Systems	(TDS). Additionally, the effect						
of transient	: heat expo	sure on th	he rate ar	nd extent of TDS drug delivery						
was concur	rently eval	uated. Tw	vo model	drug molecules, nicotine and						
fentanyl, w	vith differe	ent physic	ochemica	al characteristics (e.g. log P)						
were evalua	ated in the	current st	udy.							
		N	lethods							
In Vitro and	d In Vivo St	udies								
In vitro per	meation te	sts (IVPT)	using dei	rmatomed ex vivo human skin						
and in vivo	o pnarmac	okinetic ( rmonizod	(PK) STUO (study d	les in nealthy subjects were						
conditions	of transie	nt exposu	ire to ele	evated temperatures for two						
nicotine TD	S, 14mg/24	4h (NicoD	erm CQ <sup>®</sup>	and Aveva) and three fentanyl						
TDS, 25µg/	h (Durages)	ic <sup>®</sup> , Apotex	x and My	an). The TDS were exposed to						
one hour (ł	n) of transi	ent heat (	target ski	n temperature of 42 $\pm$ 2°C) at						
either 4 h (	early) or 8	h (late) fo	or nicotine	e TDS and at 11 h (early) or 18						
h (late) for	tentanyl TD	)S. Tempe	rature wa	is monitored using an infrared						
thermomet	er in vitro a	and a tem	perature	probe in vivo.						
<u>IVIVC</u>										
Approach I	: IVPT data	a, PK-base	d mather	matical equations and in vitro						
heat effect	coefficient	$(H_i)$ were	used to p	oredict in vivo concentrations.						
• Eq. 1 f	rediction $R_{in}$	$\cdot H_i$	was worr	1:						
	$C_s = \frac{-t\pi}{C}$	$\frac{1}{2L} \cdot (1 -$	$-e^{-\kappa\iota}$ )							
• Eq. 2 F	Prediction a	after TDS r	removal:							
	$L_s = L_0$	• e ***								
$C_s$ : Predicted	l in vivo seru	m concentr	ation	a in IV/DT avpariments)						
$H_i$ : Rate of T	heat effect of	coefficient (	composite	heat effect during and after heat						
exposure); r	atio of flux va	$H_i$ : In vitro neat effect coefficient (composite heat effect during and after heat exposure); ratio of flux value and $R_i$ until $H_i$ becomes 1 or less								
<i>CL:</i> Population total body clearance obtained from literature <sup>1,2</sup>										
CL: Populatio	on total body	/ clearance	until <i>H<sub>i</sub></i> be obtained fr	comes 1 or less fom literature <sup>1,2</sup>						
<i>CL:</i> Population <i>k</i> : Elimination <i>t</i> : Time after	on total body on constant o r administrat	/ clearance ( btained from ion of TDS f	obtained fr obtained fr m literature for Fg.1 and	comes 1 or less om literature <sup>1,2</sup> e <sup>2,3</sup> d time after removal of TDS for Eq.						
CL: Population k: Elimination t: Time after 2	on total body on constant o administrat	/ clearance btained from ion of TDS f	obtained fr obtained fr m literature or Eq.1 and	comes 1 or less rom literature <sup>1,2</sup> e <sup>2,3</sup> d time after removal of TDS for Eq.						
<i>CL:</i> Population <i>k</i> : Elimination <i>t</i> : Time after 2 <i>C</i> <sub>0</sub> : Initial con	on total body on constant o administrat	ofter TDS re	obtained fr obtained fr m literature or Eq.1 and moval	comes 1 or less rom literature <sup>1,2</sup> e <sup>2,3</sup> d time after removal of TDS for Eq.						
<i>CL:</i> Population <i>k</i> : Elimination <i>t</i> : Time after 2 <i>C</i> <sub>0</sub> : Initial cont <b>Approach I</b>	on total body on constant o administrat ncentration a	de and R <sub>in</sub> clearance btained from ion of TDS f	obtained fr obtained fr m literature or Eq.1 and moval	comes 1 or less fom literature <sup>1,2</sup> e <sup>2,3</sup> d time after removal of TDS for Eq.						
<i>CL:</i> Population <i>k</i> : Elimination <i>t</i> : Time after 2 <i>C</i> <sub>0</sub> : Initial cont <b>Approach I</b> 1. Reconst	on total body on constant o administrat ncentration a <b>Land III:</b> ruct of bas	seline (wi	thout he	comes 1 or less fom literature <sup>1,2</sup> e <sup>2,3</sup> d time after removal of TDS for Eq. at) profile by combining non-						
<ul> <li>CL: Population</li> <li>k: Elimination</li> <li>t: Time after</li> <li>2</li> <li>C<sub>0</sub>: Initial construction</li> <li>Approach II</li> <li>1. Reconstruction</li> <li>heat point</li> <li>2</li> </ul>	on total body on constant o administrat ncentration a <b>Land III:</b> ruct of bas rtion of pro	seline (wi	thout head from two stuces	comes 1 or less rom literature <sup>1,2</sup> e <sup>2,3</sup> d time after removal of TDS for Eq. at) profile by combining non- dy designs (Fig. 1)						
<ul> <li><i>CL:</i> Population</li> <li><i>k</i>: Elimination</li> <li><i>t</i>: Time after</li> <li><i>i</i>: Time after</li> <li><i>C</i><sub>0</sub>: Initial construction</li> <li>Approach II</li> <li>Reconstruction</li> <li>Approach II</li> <li>Reconstruction</li> <li>Deconvolution</li> <li>Method</li> </ul>	on total body on constant o administrat ncentration a <b>I and III:</b> ruct of bas rtion of pro olute in vi and PK pa	seline (wir of iles from of the from of the files from vo baselin rameters of	obtained fr m literature for Eq.1 and moval thout hea two stuc ne PK da obtained	comes 1 or less fom literature <sup>1,2</sup> e <sup>2,3</sup> d time after removal of TDS for Eq. at) profile by combining non- dy designs (Fig. 1) ata using the Wagner-Nelson from literature						
<ul> <li><i>CL:</i> Population</li> <li><i>k</i>: Elimination</li> <li><i>t</i>: Time after</li> <li><i>C</i><sub>0</sub>: Initial construction</li> <li>Approach I</li> <li>1. Reconstruction</li> <li><i>Approach Population</i></li> <li>1. Reconstruction</li> <li><i>Approach I</i></li> <li><i>Approach I</i>&lt;</li></ul>	on total body on constant o dministrat ncentration a <b><u>I and III:</u></b> ruct of bas rtion of pro olute in vi and PK pa ct IVIVC m	seline (wir ofiles from vo baselin rameters o	obtained fr m literature for Eq.1 and moval thout hea two stuc ne PK da obtained obtained	comes 1 or less rom literature <sup>1,2</sup> e <sup>2,3</sup> d time after removal of TDS for Eq. at) profile by combining non- dy designs (Fig. 1) ata using the Wagner-Nelson from literature raction permeated in vitro vs.						
<ul> <li>CL: Population</li> <li>k: Elimination</li> <li>t: Time after</li> <li>2</li> <li>C<sub>0</sub>: Initial constrution</li> <li>Approach II</li> <li>1. Reconstrution</li> <li>2. Deconvolution</li> <li>3. Constrution</li> </ul>	on total body on constant o diadministrat ncentration a <b><u>I and III:</u></b> ruct of bas rtion of pro olute in vi and PK pa ct IVIVC m absorbed	seline (wi ofiles from vo baselin rameters of odel by p	obtained fr m literature for Eq.1 and moval thout hea two stuc ne PK da obtained obtained	comes 1 or less rom literature <sup>1,2</sup> e <sup>2,3</sup> d time after removal of TDS for Eq. at) profile by combining non- dy designs (Fig. 1) ata using the Wagner-Nelson from literature raction permeated in vitro vs.						
<ul> <li><i>CL:</i> Population</li> <li><i>k</i>: Elimination</li> <li><i>t</i>: Time after</li> <li><i>C</i><sub>0</sub>: Initial construnct</li> <li>Approach II</li> <li>Reconstrunct</li> <li>Meat poin</li> <li>Deconvolution</li> <li>Deconvolution</li> <li>Construnct</li> <li>fraction</li> <li>Predict</li> </ul>	on total body on constant o administrat ncentration a <u>I and III:</u> ruct of bas rtion of pro olute in vi and PK pa ct IVIVC m absorbed in vivo fra	clearance btained from ion of TDS f after TDS re seline (wir ofiles from vo baselin rameters of odel by p in vivo ction abso	obtained fr m literature for Eq.1 and moval thout hea two stuc ne PK da obtained obtained obtained	comes 1 or less rom literature <sup>1,2</sup> e <sup>2,3</sup> d time after removal of TDS for Eq. at) profile by combining non- dy designs (Fig. 1) ata using the Wagner-Nelson from literature raction permeated in vitro vs. ng the IVVIC model and IVPT						
<ul> <li><i>CL:</i> Population</li> <li><i>k</i>: Elimination</li> <li><i>t</i>: Time after</li> <li><i>C</i><sub>0</sub>: Initial construnct</li> <li>Approach II</li> <li>Reconstrunct</li> <li>Meat poin</li> <li>Deconvolution</li> <li>Deconvolution</li> <li>Construnct</li> <li>fraction</li> <li>Predict</li> <li>data</li> <li>Construnct</li> </ul>	on total body on constant o administrat ncentration a <u>I and III:</u> ruct of bas rtion of pro olute in vi olute in vi and PK pa ct IVIVC m absorbed in vivo fra	clearance btained from ion of TDS f after TDS re seline (with ofiles from vo baselin rameters of odel by p in vivo ction abso	in the free obtained from literature for Eq.1 and moval thout heat thout heat two stuck obtained obtained obtained from the from the from the form	comes 1 or less rom literature <sup>1,2</sup> e <sup>2,3</sup> d time after removal of TDS for Eq. at) profile by combining non- dy designs (Fig. 1) ata using the Wagner-Nelson from literature raction permeated in vitro vs. ng the IVVIC model and IVPT						
<ul> <li><i>CL:</i> Population</li> <li><i>k</i>: Elimination</li> <li><i>t</i>: Time after</li> <li>2</li> <li><i>C</i><sub>0</sub>: Initial construnct</li> <li>Approach II</li> <li>1. Reconstrunct</li> <li>heat poin</li> <li>2. Deconvolut</li> <li>Method</li> <li>3. Construnct</li> <li>fraction</li> <li>4. Predict</li> <li>data</li> <li>5. Convolut</li> <li>6. Δροίντης</li> </ul>	on total body on constant o administrat ncentration a <u>I and III:</u> ruct of bas rtion of pro olute in vi olute in vi olute in vi and PK pa ct IVIVC m absorbed in vivo fra-	seline (wir ofiles from vo baselin rameters of odel by p in vivo ction abso	in til <i>H</i> <sub>i</sub> be obtained fr m literature for Eq.1 and moval thout hea two stuc ne PK da obtained obtained obtained obtained fr obtained usi	comes 1 or less rom literature <sup>1,2</sup> e <sup>2,3</sup> d time after removal of TDS for Eq. at) profile by combining non- dy designs (Fig. 1) ata using the Wagner-Nelson from literature raction permeated in vitro vs. ng the IVVIC model and IVPT on absorbed data heat effect coefficient (H)						
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2. Duragesic<sup>®</sup> Fentanyl Transdermal System [package insert]. Janssen Pharmaceuticals. 2014.

## Level A In Vitro/In Vivo Correlations (IVIVC) for Nicotine and Fentanyl Transdermal Delivery Systems with Transient Heat Exposure, Evaluated using Multiple Approaches Soo Hyeon Shin, Mingming Yu, Sherin Thomas, Dana C. Hammell, Hazem E. Hassan, Audra L. Stinchcomb Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, Baltimore, MD









tine. Pharmacol Rev. 57 (2005) 79-115.

3. SK Gupta, NL Benowitz, P Jacob III, CN Rolf, J Gorsline. Bioavailability and absorption kinetics of nicotine following application of a transdermal system. Br J Clin Pharmacol. 36 (1993) 221-227.



Fig 5. Comparisons of in vitro and in vivo heat effects from nicotine studies. Heat effect window was defined as 4-7 h for early heat and 8-11 h for late

Fentanyl TDS CL = 75 L/h Total CL = 51 L/h AUC CL = 27 L/h CL = 75 L/h CL = 51 L/h **C**<sub>max</sub> CL = 27 L/h **Total AUC** Cmax **Total AUC** products. PE%. highest



**Fig 9.** Comparisons of in vitro and in vivo heat effects from fentanyl studies. Heat effect window was defined as 11-14 h for early heat and 18-21 h for late heat. In vivo heat effects were higher compared to in vitro heat effects, with higher variability. (\*\*  $p \le 0.01$ , Two-way ANOVA with Bonferroni's post-hoc) 
**Table 2**. Prediction error (%) for nicotine TDS

Nicotino TDS	NicoDe	rm CQ®	Aveva							
Nicotine TD5	Early Heat	Late Heat	Early Heat	Late Heat						
Approach I										
Total AUC	4.5	6.4	31.2	5.5						
C <sub>max</sub>	10.8	8.4	38.2	6.4						
Approach II										
Total AUC	10.2	4.6	0.5	6.7						
C <sub>max</sub>	31.8	0.4	7.6	0.4						
Approach III										
Total AUC	5.1	1.2	1.1	4.5						
<b>C</b> <sub>max</sub>	15.0	5.8	8.9	17.7						

## **Table 3**. Prediction error (%) for fentanyl TDS

	Duragesic®		Арс	otex	Mylan					
	Early Heat	Late Heat	Early Heat	Late Heat	Early Heat	Late Heat				
Approach I										
1	7.5	25.3	75.8	34.0	4.9	1.8				
1	35.6	56.6	62.0	61.9	35.2	48.1				
1	193.3	335.1	396.8	395.3	191.3	264.2				
1	32.0	23.4	22.7	14.3	9.3	21.6				
	27.8	15.8	34.4	16.4	25.1	13.2				
)	332.7	124.2	187.8	125.9	152.3	117.6				
Approach II										
	7.0	0.8	8.4	23.3	1.2	14.7				
	35.2	4.5	39.1	40.4	20.3	2.6				
Approach III										
	16.5	10.1	29.3	1.4	6.5	6.0				
	7.8	2.0	16.9	26.7	8.6	41.3				

## Conclusions

The results of the in vitro and in vivo TDS heat effects studies and the different approaches to establishing a Level A correlation illustrate that carefully designed IVPT studies with nicotine and fentanyl TDS can be correlated with and predictive of in vivo heat effects for these products. The study designs, correlation approaches and analyses described here were shown to be compatible with the evaluation of multiple different TDS

Strong correlations were observed for the nicotine TDS, and the results with fentanyl TDS also showed good correlation albeit with a higher PE%. The relatively higher PE% for fentanyl may be attributable a more complex and highly variable clearance rate in vivo for fentanyl compared to nicotine, and may be impacted by a skin depot effect that has been postulated for transdermal fentanyl. Approach I, which relies only on in vitro data to make predictions without considering in vivo sources of variability showed the The other effectively two approaches, which accounted/corrected for differences in the skin permeability between the in vitro and in vivo study populations, and/or variability in the rate of clearance of the drug from the systemic circulation, generally provided a lower PE% and better predictions compared with Approach I.

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