IN VITRO-IN VIVO RELATIONSHIPS (*IVIVR*) FOR TRANSDERMAL DELIVERY OF NICOTINE FROM PATCHES

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OVERVIEW

- Transdermal delivery systems (TDS), popularly named "patches", are effective in delivering drugs through the skin for systemic effects in a precise and reproducible manner. Factors influencing drug delivery include patch design and the composition of the formulation they contain.
- *In vitro* permeation tests (*IVPT*) are increasingly used to compare drug delivery from transdermal products and to predict *in vivo* drug bioavailability (BA). This requires establishment of an *in vitro-in vivo* relationship (*IVIVR*): "a predictive mathematical model to describe the relationship between an *in vitro* property and a relevant *in vivo* response of a drug product" [1].
- So far, few studies have explored *IVIVR* for these systems and regulatory guidance for establishment of *IVIVR* for TDS is not yet available.

AIM & METHODS

Aim:

1. Derive inter- and intra-subject variability and 90% prediction intervals from population modelling of experimental nicotine *IVPT* data for commercial nicotine TDS.
2. Develop a point-to point (Level-A) *IVIVR* between *IVPT* data and *in vivo* data obtained from published human studies [2-5].
3. Explore circadian and meal effects on predicted nicotine plasma concentrations.

Method:

IVPT studies were performed for four different marketed formulations of nicotine TDS (**Table 1**). Patches were trimmed to 3.14 cm^2 and adhered to the stratum corneum of heat separated human epidermis (n=4) mounted in Franz-type diffusion cells (1.3 cm^2). Nicotine permeation was monitored over 24 h.

Table 1 Characteristics of nicotine TDS used in the study

	Nicotine TDS (21 mg/24 h)		Nicotine TDS (15 mg/16 h)	
	Nicabate	Nicotinell	Nicorette Invisipatch	Nicorette
TDS size (cm^2)	22	30	13.5	30
Total nicotine content (mg)	114	52.5	23.62	24.9
***In vivo* delivery per application (mg)**	21	21	15	15
Delivery Rate (µg/cm^2/h)	40	29	46.3	21
Type	membrane controlled	matrix	matrix	matrix

IVPT data were first analysed by a population approach using ADAPT5; data were then convoluted with intravenous bolus human data for nicotine [6] to predict the *in vivo* plasma concentration profile. A Level-A *IVIVR* was explored by Prediction Error (% PE) as well as deconvolution data (**Figure 1**).

The effects of circadian variation and meals on nicotine clearance (CL) and consequently on predicted nicotine plasma concentrations were also examined.

$$CL(t) = [constant\ baseline\ clearance + circadian\ (t)] * [1 + meal\ (t)]$$

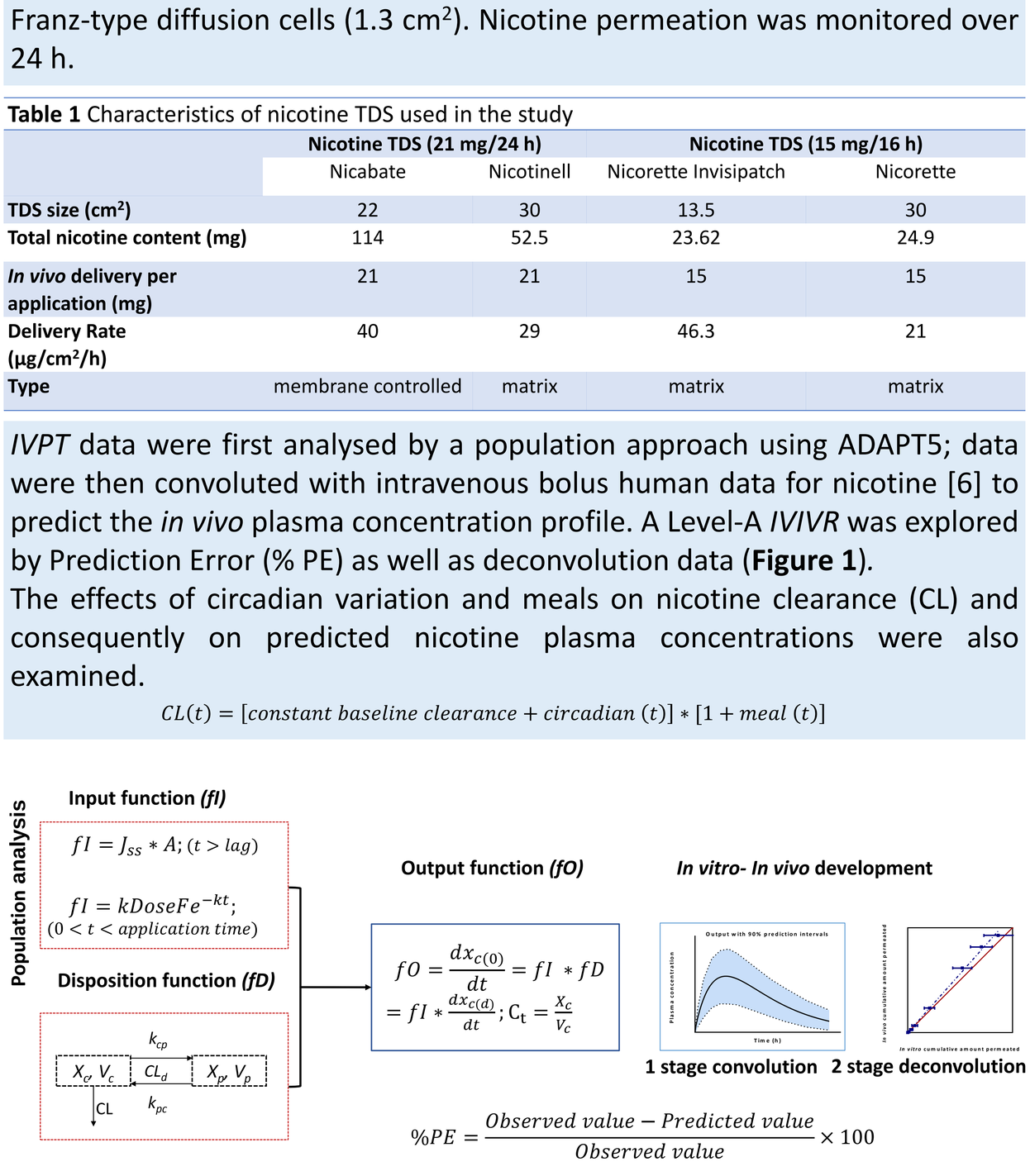

Figure 1 Schematic representation of simulation of plasma drug concentration from *IVPT* data, *IVIVR* development and the equation of % PE are included.

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RESULTS & DISCUSSION

Nicabate and Nicorette displayed first-order skin permeation while Nicotinell and Nicorette Invisipatch displayed zero-order skin permeation kinetics (**Figure 2**). Nicorette Invisipatch showed the highest intra and inter-subject variability compared to other patches (**Figure 2**, column right).

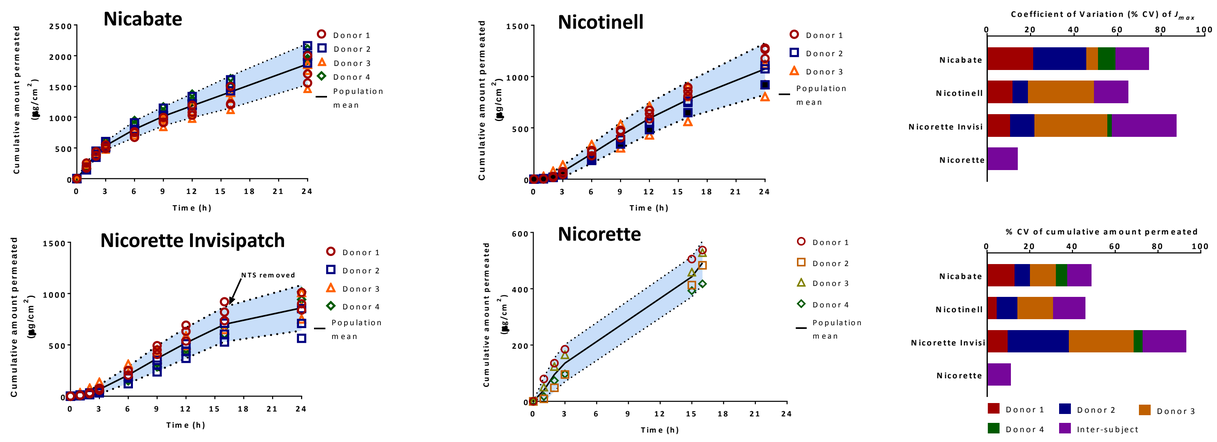
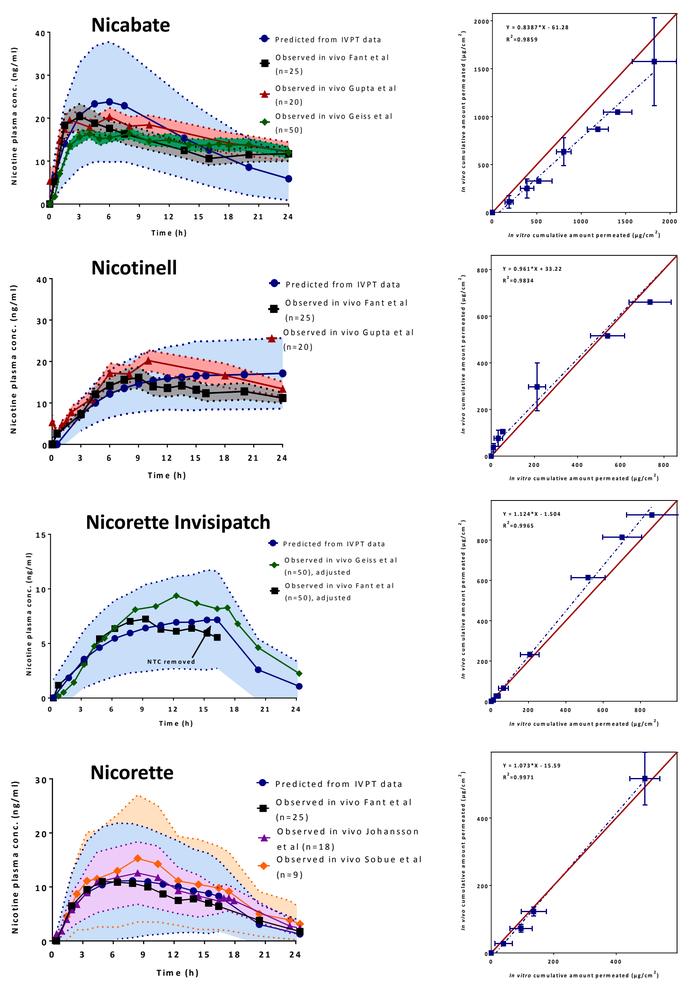


Figure 2: *IVPT* data of different TDS with 90% population intervals shown in blue shades, Intra-subject and inter-subject variability of J_{max} and cumulative amount permeated are shown as % CV.



The predicted *in vivo* plasma concentration from *IVPT* correlated well with the *in vivo* literature data. Linear relationships between *in vivo* and *in vitro* cumulative amounts with a slope of unity were observed compared to the predicted *in vivo* results (**Figure 3**).

An average absolute % PE of ≤ 10% for C_{max} and AUC_{last} established the predictability of the Level A *IVIVR* (**Table 2**).

Figure 3 Level-A *IVIVR*, left column, one stage *IVIVR* of nicotine plasma concentration predicted from *IVPT* versus time with 90% prediction intervals in blue shading and 90% confidence interval of *in vivo* data. Right column, 2 stage *IVIVR* cumulative amount permeated deconvoluted from *in vivo* studies versus values from *IVPT* ± standard deviation.

Table 2 The percent of prediction errors for (Area Under the Curve) AUC_{last} and C_{max} values

NTDS name	AUC_{last} (observed)	AUC_{last} (predicted)	% PE	C_{max} (observed)	C_{max} (predicted)	% PE
Nicabate	330.37	362.04	-9.59	20.40	23.79	-16.61
Nicotinell	289.06	325.36	-12.56	16.10	17.14	-6.46
Nicorette	135.78	147.48	-8.62	10.87	11.15	-2.56
Nicorette invisipatch	102.12 85.84	85.23	16.54 0.72	9.38 7.245	7.17	23.5 1.06

The effect of meal on the prediction of nicotine plasma concentration was more pronounced compare to the circadian effect (**Figure 4**).

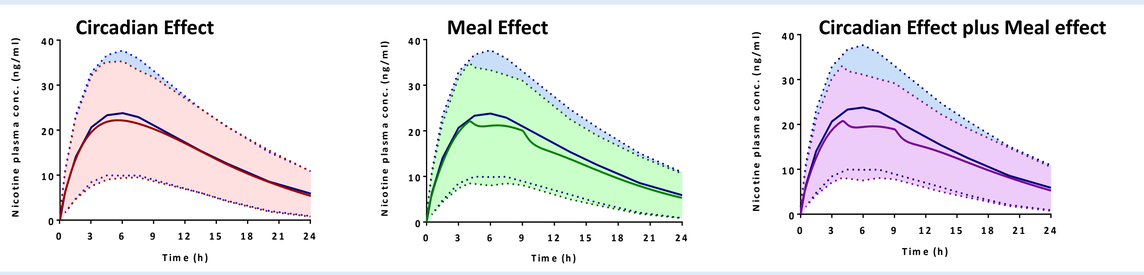


Figure 4 Simulated nicotine plasma concentration versus time from *IVPT* data of Nicabate. Blue colour shows the time-invariant prediction, meal and circadian effects shown in different colours.

CONCLUSION

We developed a strong Level-A *IVIVR* between predicted plasma nicotine concentrations from *IVPT* studies and *in vivo* values in both convolution and deconvolution stages in humans. *IVPT* studies can be used as a surrogate of *in vivo* studies for product development and characterization. Meal effect on the prediction of nicotine plasma concentration needs to be considered.

References

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