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In vitro–in vivo correlations for nicotine transdermal delivery systems evaluated by both *in vitro* skin permeation (IVPT) and *in vivo* serum pharmacokinetics under the influence of transient heat application

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ABSTRACT

The *in vitro* permeation test (IVPT) has been widely used to characterize the bioavailability (BA) of compounds applied on the skin. In this study, we performed IVPT studies using excised human skin (*in vitro*) and harmonized *in vivo* human serum pharmacokinetic (PK) studies to evaluate the potential *in vitro–in vivo* correlation (IVIVC) of nicotine BA from two, matrix-type, nicotine transdermal delivery systems (TDS). The study designs used for both *in vitro* and *in vivo* studies included 1 h of transient heat (42 ± 2 °C) application during early or late time periods post-dosing. The goal was to evaluate whether any IVIVC observed would be evident even under conditions of heat exposure, in order to investigate further whether IVPT may have the potential to serve as a possible surrogate method to evaluate the *in vivo* effects of heat on the bioavailability of a drug delivered from a TDS. The study results have demonstrated that the BA of nicotine characterized by the IVPT studies correlated with and was predictive of the *in vivo* BA of nicotine from the respective TDS, evaluated under the matched study designs and conditions. The comparisons of single parameters such as steady-state concentration, heat-induced increase in partial AUCs and post-treatment residual content of nicotine in TDS from the *in vitro* and *in vivo* data sets showed no significant differences ($p \geq 0.05$). In addition, a good point-to-point IVIVC (Level A correlation) for the entire study duration was achieved by predicting *in vivo* concentrations of nicotine using two approaches: Approach I requiring only an *in vitro* data set and Approach II involving deconvolution and convolution steps. The results of our work suggest that a well designed IVPT study with adequate controls can be a useful tool to evaluate the relative effects of heat on the BA of nicotine from TDS with different formulations.

1. Introduction

Drug delivery from transdermal delivery systems (TDS) has been studied extensively over several decades. The existing scientific literature has greatly advanced our understanding of the skin barrier, and of the considerations related to drug molecules and drug product formulations that can influence transdermal delivery [1–3]. While research efforts have predominantly focused on improving drug delivery from TDS, a substantial body of work has focused on studying the influence of external factors, such as heat, on drug delivery from TDS. The effect of temperature on the delivery of molecules through skin has been explored since the early work of Blank et al. in 1967 [4,5]. Since then, the effects of heat have been used to enhance drug delivery from TDS, as in the case of the lidocaine/tetracaine heat-assisted topical patch, Synera®, and other products using heat-assisted drug delivery are reportedly under development [6]. While TDS may be designed to

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function with controlled heat that modulates its performance, the application of heat to a TDS that was not designed to be used at elevated temperatures may lead to unintended consequences, most likely associated with an (initial) increase in the rate and extent of drug delivery. Multiple such incidents have been reported, including life-threatening toxicities, from an overdose of fentanyl from a fentanyl TDS [7–10]. Consequently, the United States Food and Drug Administration (FDA) issued a warning about life threatening side effects related to the application of heat or exposure to high body temperatures for the fentanyl TDS [11].

There have been several *in vitro* and *in vivo* studies investigating the effects of heat on drug delivery from TDS [12–18]. These studies have clearly demonstrated that heat increases the bioavailability (BA) of drugs from various TDS. However, appropriate methods by which to evaluate the relative extent of heat effects on different TDS have not been established. The development and validation of such methods would be valuable for comparing heat effects on various TDS with different formulations, which would be of particular utility for comparing heat effects on brand name and generic TDS. Since clinical studies are costly, time consuming, and may expose subjects to risks associated with elevated levels of exposure to some drugs, it would be of great value to develop a robust *in vitro* method that can serve as a surrogate for *in vivo* pharmacokinetic (PK) studies to compare the effects of heat on the BA of a drug from a TDS. The *in vitro* permeation test (IVPT) model has been widely studied and frequently compared with *in vivo* results, and when *in vitro* and *in vivo* study designs are harmonized, the BA of compounds applied to the skin evaluated by IVPT studies has correlated well with the BA observed *in vivo* [19]. Previous studies have utilized the IVPT model specifically to examine the effect of heat on the BA of a drug from various TDS with dissimilar formulations, using excised porcine skin [20]. The first aim of the current study was to further evaluate the IVPT model using excised human skin, as a possible surrogate method to compare heat effects on the *in vivo* BA of nicotine (as a model drug) from two pharmaceutically equivalent nicotine TDS products that have different formulations (the two products are not expected to be bioequivalent to each other). The second aim was to evaluate whether there was an *in vitro–in vivo* correlation (IVIVC) that could be established between the IVPT and human *in vivo* PK data sets, obtained under matched study designs using five different methods, including two approaches for developing Level A IVIVC to describe a point-to-point relationship between *in vitro* and *in vivo* data sets for the entire duration of the study designs.

2. Materials and methods

2.1. Materials and study products

L-Nicotine 99 + % (Acros Organics), sodium chloride, methanol, acetonitrile, triethylamine, ethyl acetate and ammonium formate were purchased from Fisher Scientific Inc. (Fair Lawn, NJ). Nicotine hydrogen tartrate salt and cotinine reference standards were purchased from Sigma Aldrich (St. Louis, MO). Nicotine-D_4 and cotinine-D_3 were purchased from Cerilliant Corporation (Round Rock, TX). All reagents were of analytical grade or better. Nanopure water was supplied in-house by a Milli-Q® system (EMD Millipore; Billerica, MA).

The two nicotine TDS products that were used in both *in vitro* and *in vivo* studies were purchased from Amazon.com, Inc. (Seattle, WA). The two TDS from different manufacturers were both nicotine transdermal extended release film 14 mg/24 h TDS drug products: One of the two nicotine TDS is marketed under the proprietary name "NicoDerm CQ®" with a National Drug Code (NDC) of 0135-0195-02 (Sanofi Aventis US LLC). The other nicotine TDS is marketed under NDC 0536-5895-88 (Aveva drug delivery systems). While these two over-the-counter matrix-type TDS products have the same nominal nicotine delivery rate of 14 mg/24 h, they differ in design (size) and formulation (adhesive type and other inactive ingredients) and are not listed in the Orange Book as being therapeutically equivalent to each other (Table 1) [21]. Since both products have the same, lengthy established name (nicotine transdermal extended release film, 14 mg/24 h) but differ notably in adhesive type (among other product attributes), the products are differentiated in this article by codified names. The NicoDerm CQ® nicotine TDS, which has a polyisobutylene adhesive, is referred to as "N-Pol", and the Aveva nicotine TDS, which has acrylate and silicone adhesives, is referred to as "A-Sil".

Table 1
Characteristics of nicotine TDS used in the study.

	Nicotine TDS (14 mg/24 h)	
	N-Pol (NicoDerm CQ®)	A-Sil (Aveva)
TDS size (cm^2)[a]	15.75	20.12
Rate/area (μg/h/cm^2)	37	29
Inactive ingredients	Ethylene vinyl acetate-copolymer, polyisobutylene and high density polyethylene between pigmented and clear polyester backings	Acrylate adhesive, polyester, silicone adhesive

[a] TDS sizes measured due to unavailability of the information on package labels.

2.2. IVPT studies

2.2.1. Human skin preparation

Human skin from four individuals (donors), harvested with consent during abdominoplasty surgery, was obtained from the Cooperative Human Tissue Network, deidentified, and used for *in vitro* experiments. A summary of the demographic features of the four donors is presented in Table 2. The fresh skin samples were dermatomed to a thickness of 260 ± 40 μm, removing subcutaneous fat and keeping the outer layers of skin containing stratum corneum, viable epidermis and some dermis intact. The dermatomed skin was stored at − 20 °C until used. On the day of the experiment, skin was cut into a 4.84 cm^2 square to fit onto the diffusion cell and thawed for at least 30 min prior to use. The barrier integrity of each skin piece was tested by measuring transepidermal water loss (TEWL) using a cyberDERM RG-1 open chamber evaporimeter (cyberDERM, Inc.; Broomall, PA) prior to the diffusion experiment. Any skin piece with obvious signs of physical damage or a TEWL reading higher than 15.0 g/m^2/h was excluded from the experiment. The maximum value of 15 g/m^2/h for TEWL was determined internally based on our research group's experience and is also in line with reported TEWL levels in healthy skin (0–15 g/m^2/h) [22]. The mean (SD) TEWL value of all skin pieces used for this study was 3.78

Table 2
Demographic information for *in vitro* study donors and *in vivo* PK study subjects.

	In vitro donors (n = 4)	*In vivo* subjects (n = 10)
Age in years		
Mean (SD)	57.3 (11.4)	30.0 (6.3)
Range	47–69	24–44
Sex, n (%)		
Male	0 (0)	7 (70)
Female	4 (100)	3 (30)
Ethnicity, n (%)		
Black	2 (50)	9 (90)
Black/Caucasian	0 (0)	1 (10)
Caucasian	2 (50)	0 (0)
BMI (kg/m^2)		
Mean (SD)	Unknown	22.5 (1.5)
Range		20.8–24.9