508237

Assessment of the Bioavailability of Rivastigmine from Two Rivastigmine Transdermal Delivery Systems with and without Exposure to Heat Using an In Vitro Permeation Test (IVPT)

Qingzhao Zhang[1], Priyanka Ghosh[2], Sam G. Raney[2], Dana C. Hammell[1], Hazem E. Hassan[1], Audra L. Stinchcomb[1]

[1]Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, Baltimore, MD

[2]Division of Therapeutic Performance, Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. FDA, Silver Spring, MD

CONTACT INFORMATION: qzhang@umaryland.edu

aaps PharmSci 360 ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

PURPOSE

Rivastigmine is used to treat mild to moderate dementia related to Alzheimer's and Parkinson's disease and is available in oral capsules and transdermal delivery systems (TDS). Exposure to heat (elevated temperature) may alter the bioavailability of rivastigmine from a TDS. Such changes in bioavailability may be largely dependent on the design and composition of the TDS. Therefore, the effect of controlled heat on the comparative bioavailability of rivastigmine from a reference and generic rivastigmine TDS, which are different in composition, was investigated in this study.

OBJECTIVE(S)

1) Explore the feasibility of using an in vitro permeation test (IVPT) to characterize the rate and extent of rivastigmine permeation.
2) Optimize the IVPT study conditions for evaluating the delivery of rivastigmine across human skin using an IVPT study, and to characterize the effects of heat on the transdermal delivery of rivastigmine through human skin in vitro.

METHOD(S)

EXELON® (rivastigmine) TDS, 9.5 mg/24 h (reference listed drug (RLD)), and a generic TDS, 9.5 mg/24 h (Alvogen) were evaluated. IVPT studies were conducted using a PermeGear® In-Line flow-through diffusion cell system (Figure 1). 0.97 cm^2 discs of each TDS were applied onto a 0.95 cm^2 area of d ermatomed porcine or human skin samples with transepidermal water loss values below 15.0 $g/m^2/h$. Studies were performed either at a normal skin surface temperature (32 ± 2°C), or under continuous or transient exposure to elevated skin surface temperature (42 ± 2°C). Temperature at the surface of the skin was maintained using a circulating water bath. Isotonic phosphate buffer (pH 7.4 ± 0.1) was used as the receiver solution at a flow rate of 1.0 mL/h and samples were collected at pre-determined time intervals.

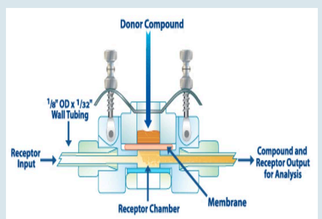

Figure 1. Cross-sectional view of an In-Line Cell with HPLC fittings (Source: PermeGear, http://www.permegear.com/inline.htm)

Concentrations of rivastigmine in the receiver solution were analyzed using a validated high performance liquid chromatography (HPLC) method. Flux profiles were generated based on the concentration of rivastigmine in receiver solution collected across the 24 h study duration. Each study condition was evaluated using four replicate skin sections per TDS. Statistical analyses were conducted using an unpaired t test (GraphPad Prism 7).

RESULT(S)

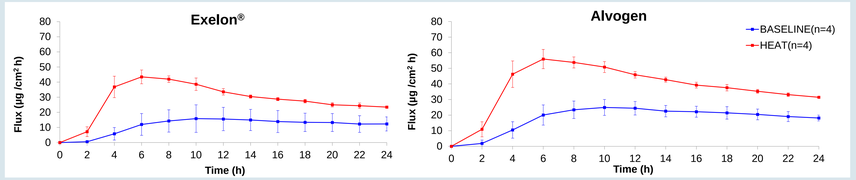

Figure 1 Study I Flux values (µg/cm^2·h) at baseline and continuous heat (24 h) conditions (n=4 replicates/treatment) [Mean ± SD, **porcine skin**] for EXELON® TDS (left) and Alvogen's rivastigmine TDS (right). Time points obtained: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 h

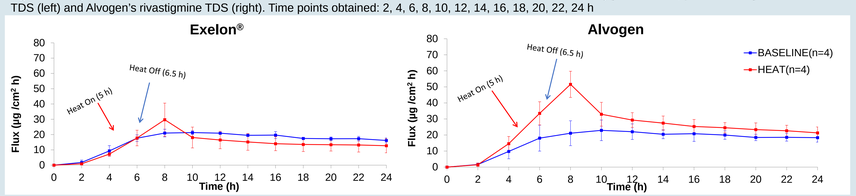

Figure 2 Study II Flux values (µg/cm^2·h) at baseline and transient heat (1.5 h) conditions (n=4 replicates/treatment) [Mean ± SD, **porcine skin**] for EXELON® TDS (left) and Alvogen's rivastigmine TDS (right). Time points obtained: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 h

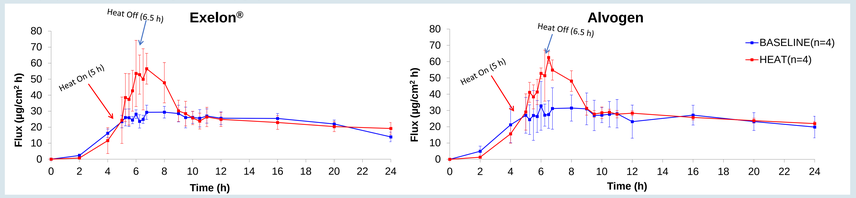

Figure 3 Study III Flux values (µg/cm^2·h) at baseline and transient heat (1.5 h) conditions (n=4 replicates/treatment) with additional timepoints during heat treatment [Mean ± SD, **porcine skin**] for EXELON® TDS (left) and Alvogen's rivastigmine TDS (right). Time points obtained: 2, 4, 5, 5.25, 5.5, 5.75, 6, 6.25, 6.5, 6.75, 8, 9, 9.5, 10, 10.5, 11, 12, 16, 20, 24 h

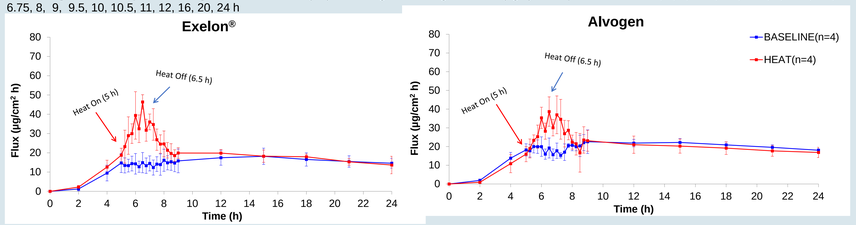

Figure 4 Study IV Flux values (µg/cm^2·h) at baseline and transient heat (1.5 h) conditions (n=4 replicates/treatment) [Mean ± SD, **human skin donor 1**] for EXELON® TDS (left) and Alvogen's rivastigmine TDS (right). Time points obtained: 2, 4, 5, 5.25, 5.5, 5.75, 6, 6.25, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 12, 15, 18, 21, 24 h

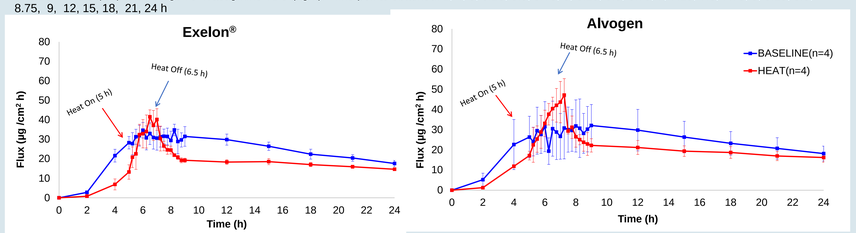

Figure 5 Study V Flux values (µg/cm^2·h) at baseline and transient heat (1.5 h) conditions (n=4 replicates/treatment) [Mean ± SD, **human skin donor 2**] for EXELON® TDS (left) and Alvogen's rivastigmine TDS (right). Time points obtained: 2, 4, 5, 5.25, 5.5, 5.75, 6, 6.25, 6.5, 6.75, 7, 7.25, 7.5, 7.75, 8, 8.25, 8.5, 8.75, 9, 12, 15, 18, 21, 24 h

Exelon® TDS

Study	Baseline (x)	Heat (y)	Enhancement (y/x)	#*p* value
I	15.85 ± 9.12 (10 h)	43.46 ± 4.56 (6 h)	2.74	0.0026
II	21.31 ± 1.31 (10 h)	29.73 ± 10.86 (8 h)	1.395	0.2708
III	29.36 ± 3.66 (8 h)	56.51 ± 9.61 (6.75 h)	1.92	0.0207
IV	18.19 ± 4.24 (15 h)	46.40 ± 3.75 (6.5 h)	2.55	<0.0001
V	34.82 ± 2.95 (8.25h)	41.58 ± 3.56(6.5 h)	1.19	0.0047

Rivastigmine TDS (Alvogen)

Study	Baseline (x)	Heat (y)	Enhancement (y/x)	#*p* value
I	24.92 ± 5.10 (10 h)	55.94 ± 6.16 (6 h)	2.25	0.0001
II	22.91 ± 6.41 (10 h)	51.58 ± 8.17 (8 h)	2.252	0.0019
III	31.49 ± 8.02 (8 h)	62.54 ± 3.62 (6.5 h)	1.99	0.0091
IV	22.59 ± 6.30 (9 h)	38.69 ± 7.86 (6.5 h)	1.71	0.0314
V	32.09 ± 10.4 (9 h)	47.18 ± 8.15 (7.25 h)	1.47	0.0491

Table 1. Heat-induced enhancement in J_{max} for EXELON® TDS (top) and Alvogen's rivastigmine TDS (bottom). Study I-III: porcine skin donor. Study IV& V: human skin donor

CONCLUSION(S)

Both the generic and RLD TDS exhibited an increase in the rate and extent of drug delivery in vitro when exposed to an elevated temperature, involving continuous or transient heat. The time to reach J_{max} was also shorter for both TDS, relative to baseline condition, when heat was applied. Results suggest that carefully designed and optimized IVPT studies using excised human skin may have the potential to compare changes in the rate and extent of drug delivery from generic and RLD rivastigmine TDS under the influence of heat. Additional studies using an identical study design but different donors (human skin) are currently underway. The data from all the in vitro studies will be used to evaluate an in vitro-in vivo correlation between IVPT and serum pharmacokinetic data from human subjects, and help evaluate the effectiveness of an IVPT study as a tool for comparing bioavailability of rivastigmine from different rivastigmine TDS under the influence of heat.

ACKNOWLEDGEMENT

Funding for this project was made possible, in part, by the Food and Drug Administration through grant U01FD004955. The views expressed in this poster do not reflect the official policies of the U.S. Food and Drug Administration or the U.S. Department of Health and Human Services; nor does any mention of trade names, commercial practices, or organization imply endorsement by the United States Government.

FDA U.S. FOOD & DRUG ADMINISTRATION

UNIVERSITY of MARYLAND SCHOOL OF PHARMACY