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Effect of Adhesion on Pharmacokinetics (PK) of Transdermal (TDS) Topical Products

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PURPOSE

- The drug delivered into the bloodstream through the skin from a Transdermal Delivery System (TDS) should be proportional to the surface area over which the drug delivery occurs.
- Therefore, it is logical to expect that as a TDS partially loses its adherence to the skin, the ***reduction*** in the surface area of contact should, in theory, proportionally diminish the amount of drug delivered from the TDS.
- Yet, historical results from pharmacokinetic (PK) studies involving TDS that detach to varying degrees over the duration of wear did ***not*** provide clear evidence to support this expectation.
- However, several issues ***confounded*** the available TDS adhesion/PK data, like the fact that PK sampling was often stopped when TDS began to detach substantially, making available results difficult to interpret.
- In June of 2016, the FDA published a draft Guidance for Industry recommending that PK samples continue to be collected and analyzed from all subjects at all sampling times irrespective of the TDS adhesion score (even after complete detachment)[1].
- In several studies subsequently submitted in abbreviated new drug applications (ANDAs), both ***PK*** and ***adhesion scores*** were collected throughout the study.
- This allows us to evaluate the effect of adhesion/detachment on the PK of TDS products.

OBJECTIVES

To systematically evaluate the ***association*** between ***PK*** and ***adhesion*** in the selected ANDA studies. In particular,

- To evaluate whether ***summary*** PK parameters (Cmax, AUC_{inf}, AUC_t) are significantly associated with ***summary*** adhesion performance (weighted mean adhesion score) in the PK bioequivalence (BE) studies.
- To confirm the association between summary PK parameters and summary adhesion performance at the individual level: whether ***individual*** bioavailability (BA) at each time point is associated with the performance of ***individual*** adhesive measurement at each time point for a TDS.

METHODS

- Fourteen two-way cross-over PK BE studies with both plasma concentrations and adhesion scores (specifically those with severe detachment) measured simultaneously, with no taping allowed, were analyzed.
- Five TDS products (two to five ANDAs per drug product) were investigated.
- For each drug product, linear mixed models were used to assess the association between PK parameters and the mean adhesion score based on the original adhesion data without imputation, after adjusting for study design variables (sequence, period, and treatment), and incorporating the variability between treatments within the same subject.
- Summary PK parameters vs. summary mean adhesion scores were plotted for each TDS product.
- The association between the summary PK parameters (for drug absorption) and the summary adhesion parameters (mean adhesion scores) was further verified by plotting individual plasma concentration value against individual adhesion score at each sampling time for each TDS product.

RESULTS

Our analysis reveals that,

- Mean adhesion score was ***significantly*** associated with the extent of drug absorption, reflected by the PK parameters AUC_t and AUC_{inf}, in ***four*** of ***five*** TDS products evaluated: A ***higher*** mean adhesion score (i.e., greater detachment) was associated with a ***lower*** level of AUC_t or AUC_{inf} (beta<0, P<0.05) noted in Table 1.
- The association between the mean adhesion score and C_{max} was significant for ***three*** of the TDS products evaluated: ***Drug 1, Drug 2 and Drug 4.***

Table 1. Effect of Mean Adhesion Score on PK Parameters by Drug (Beta: effect of one unit increase in mean adhesion score on PK parameter)

Drug Name	$LogAUC_t$		$LogAUC_{inf}$		$LogC_{max}$	
	Beta (standard error)	P value	Beta (standard error)	P value	Beta (standard error)	P value
Drug 1	-0.080 (0.03)	**0.0081**	-0.077 (0.03)	**0.0111**	-0.079 (0.03)	**0.0239**
Drug 2	-0.362 (0.06)	**<.0001**	-0.343 (0.06)	**<.0001**	-0.296 (0.08)	**0.0004**
Drug 3	-0.097 (0.02)	**<.0001**	-0.085 (0.02)	**<.0001**	-0.011 (0.03)	0.6787
Drug 4	-0.329 (0.10)	**0.0014**	-0.340 (0.09)	**0.0004**	-0.326 (0.11)	**0.0037**
Drug 5	0.035 (0.03)	0.3316	-0.003 (0.03)	0.9134	0.035 (0.03)	0.2527

Figure 1. $LogAUC_t$ Vs. Mean Adhesion Score by Drug (Blue: Linear; Red: Loess)

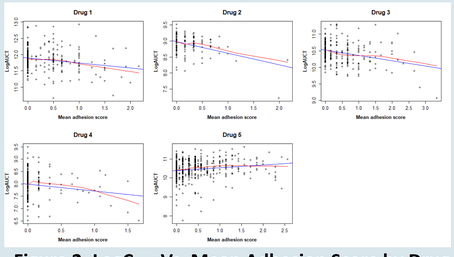
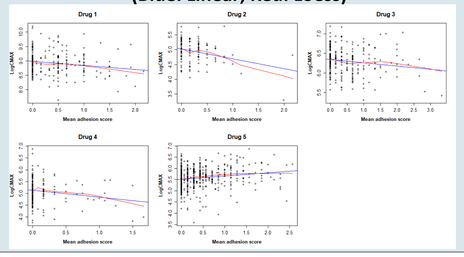
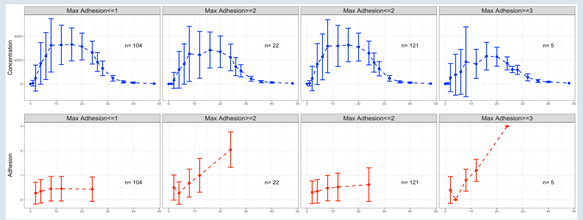


Figure 2. $LogC_{max}$ Vs. Mean Adhesion Score by Drug (Blue: Linear; Red: Loess)



- A ***side by side*** plot of the individual plasma concentration and individual adhesion scores did ***not*** reveal a clear trend.

Figure 3. Drug 1 (Representative Data) Plasma Concentration (Blue Upper) and Adhesion Score (Red Lower) vs. Time by Maximum Adhesion Score <2 vs. ≥2 and <3 vs. ≥3



- However, when taking into account the ***temporal*** (ADME) effect by plotting plasma concentration vs. adhesion scores at each time point, a ***higher*** individual adhesion score (***greater detachment***) was associated with a ***low***er blood concentration level at most time points, especially at the ***later*** ones.

Figure 4. Drug 1: Drug Concentration by Adhesion Score at Each Assessment

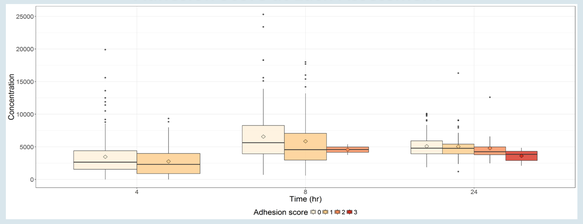


Figure 5. Drug 2: Drug Concentration by Adhesion Score at Each Assessment

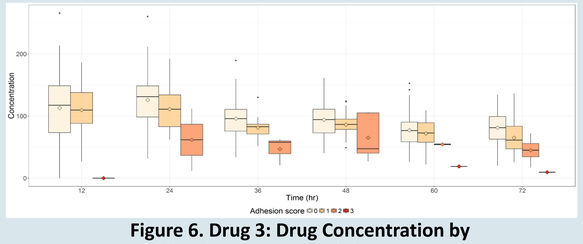


Figure 6. Drug 3: Drug Concentration by Adhesion Score at Each Assessment

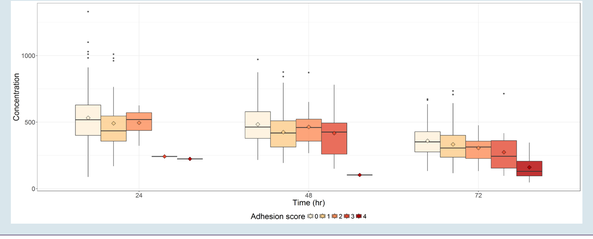


Figure 7. Drug 4: Drug Concentration by Adhesion Score at Each Assessment

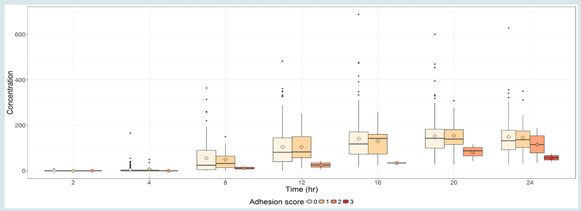
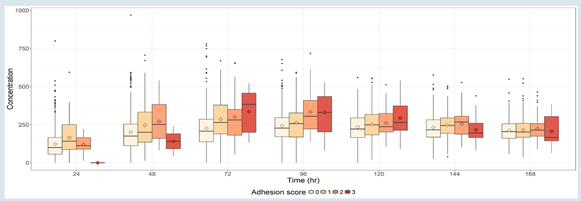


Figure 8. Drug 5: Drug Concentration by Adhesion Score at Each Assessment



CONCLUSIONS

- Our results, based on fourteen studies encompassing five TDS products with both PK and adhesion data collected continuously, even as TDS detached, provides the ***first*** demonstration of a possible ***trend*** between TDS detachment and a corresponding decline in bioavailability.
- In general, a ***larger*** surface area of contact for the TDS was significantly associated with correspondingly ***higher*** AUC values, and less significantly with the corresponding C_{max} values (the latter was likely less significant because substantial TDS detachment typically occurs later during product wear, usually after C_{max} is achieved) (Table 1).
- The findings also illustrate that our ***novel*** approach to the analysis of the results was critical in order to uncover the underlying ***association*** between PK parameters and TDS adhesion performance, at both the summary (Table 1, Figures 1-2) and the individual levels (Figures 4-8).
- In particular, correction for the ***temporal*** component is important in order to deconvolute the relationship between PK and TDS adhesion, and needs to be taken in consideration for such analyses (Figures 4-8).
- As more datasets become available, further analysis with paired PK and adhesion results is warranted, in order to verify the apparent trends revealed in this work.

REFERENCE

- FDA draft guidance for industry: Assessing adhesion with transdermal delivery systems and topical patches for ANDAs, June 2016

DISCLAIMER AND ACKNOWLEDGEMENT

- The opinions and information in this poster are those of the authors, and do not represent the views and/or policies of the U.S. Food and Drug Administration.

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