Role of Surface Morphological Characteristics of Substrate in Adhesion Performance of Topical and Transdermal Delivery Systems (TDS)

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PURPOSE

The adhesion to skin of topical and transdermal delivery systems (TDS) is a critical product performance attribute. Adhesion performance may be influenced by factors intrinsic to the TDS (such as the formulation), or extrinsic (such as skin properties and environmental conditions). Current TDS adhesion performance assessments ultimately rely on in vivo adhesion studies with human subjects, and there is a need for more efficient, predictive, in vitro test methods. Existing in vitro adhesion tests typically use polished stainless steel or high-density polyethylene substrates that are not representative of skin properties and that do not emulate clinically relevant extrinsic factors. This work aims to develop skin mimetic substrates and evaluate how topographical features impact TDS adhesion performance in vitro, because skin surface morphological characteristics such as topography may be a critical factor impacting the clinical adhesion performance of TDS products.

METHODS

Polymeric substrates were cast using 3D printed molds that were designed using AutoCAD (Figure 1) to have varied topography levels (M-T0 to M-T4, low to high). Commercial materials (in this case referred to as DS 40:60) were used to manufacture the substrates. Micro-topographical features of the DS 40:60 substrates (n=3) were observed using a LEXT microscopic system (Olympus LEXT OLS4100, EVIDENT, Japan). Substrates were characterized for elasticity, hardness and contact angle. Adhesion performance of an over-the-counter (OTC) TDS product (US-NicoDerm, 45 mm × 45 mm) (n=2) was assessed using DS 40:60 substrates and the stainless-steel substrate. The adhesion performance was assessed with a novel peel adhesion test we developed using a texture analyzer (Brookfield CTX, AMETEK Brookfield, USA) with a standardized TDS attachment force and a 5 mm/s peel rate at 180°. The force required to peel the TDS from each substrate was measured, and the area under the force-time curve (workload) representing the peel resistance was also calculated.

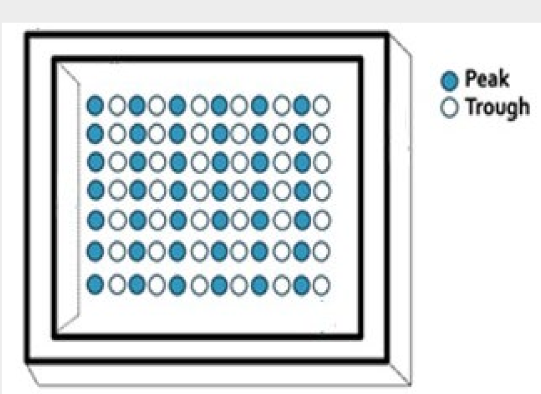


Figure 1. The developed AutoCAD design schematic of peak and trough topographical elements of the substrate casting molds (M-T1 to M-T4). M-T0 is control level with no peak or trough. Peak and trough diameters increase from M-T1 to M-T4.

RESULTS

1. 3D-printed molds for substrate casting

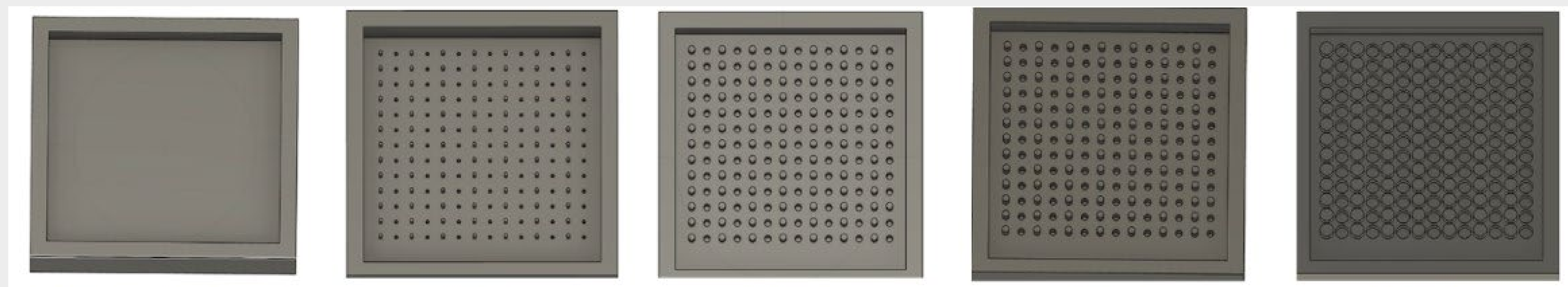


Figure 2. 3D Auto-CAD images of the designed molds for casting substrates with topographical levels from low to high including M-T0 (control level, no peak or trough), M-T1 (level 1), M-T2 (level 2), M-T3 (level 3), M-T4 (level 4).

2. Characterization of casted substrates

Measured topographic indices of developed DS 40:60 substrates M-T1 to M-T4 increased when compared to M-T0 (**Figure 3**), indicating that the incorporation of peaks and troughs led to a rougher and less uniform surface on the substrates.

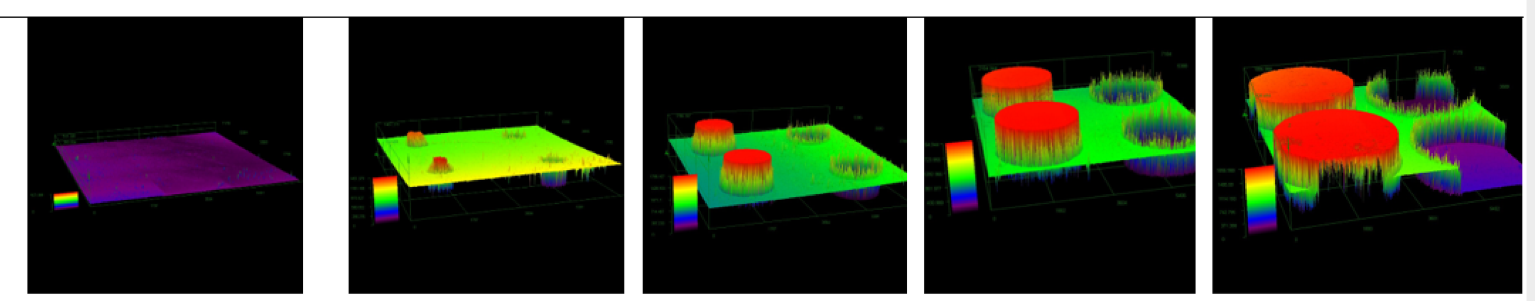
Substrate Code		DS40:60 M-T0 (Control)	DS40:60 M-T1	DS40:60 M-T2	DS40:60 M-T3	DS40:60 M-T4
Images captured by LEXT						
Topographical indices	Sa [µm]	6.37±0.94	46.01±3.03	54.41±3.08	55.21±1.79	46.97±2.84
	Sz [µm]	56.61±5.53	462.64±36.28	619.76±24.21	629.45±40.27	586.17±60.78

Figure 3. Microscopic LEXT images of developed DS 40:60 substrates incorporated with topographical levels (M-T0 to M-T4) and measured topographical parameters (n=3), including Sa (arithmetic mean of height) and Sz (sum of maximum peak height and maximum valley depth) of the developed substrates. Sa and Sz are shown as mean ± standard deviation.

The physical properties across the DS 40:60 substrates were similar eliminating these as confounding factors when interpreting the substrate topography-peel adhesion relationship across the DS 40:60 substrates. However, addition of topographical features (dots) led to a reduction in overall density of the substrates impacting their elasticity and hardness as observed in **Table 1**.

***Table 1.** Measured physical properties of 5 developed DS 40:60 substrates incorporated with topographical levels (M-T0 to M-T4, low to high) (n=3).*

Substrate code		DS40:60 M-T0	DS40:60 M-T1	DS40:60 M-T2	DS40:60 M-T3	DS40:60 M-T4
Elasticity (Tensile test)	Peak load (g)	934.9±193.6	629.8±30.8	715.9±51.2	673.7±67.8	821.4±44.8
	Workload (mJ)	179.7±38.8	110.0±7.8	128.4±13.7	127.3±16.4	154.2±5.3
Hardness (Compression test)	Peak load (g)	10.9±0.4	10.7±0.2	6.4±1.4	6.8±2.4	6.4±1.1
	Workload (mJ)	652.5±9.2	665.7±4.9	442.0±91.4	470.0±154.6	444.3±76.2
Contact angle (°)		99 ± 0.5	-	-	-	-

3. Adhesion testing

Peel adhesion results of the OTC TDS product attached on the DS 40:60 substrates and stainless-steel substrate are presented in **Figure 4**. Based on the limited data (n=2), as topography level increased from DS 40:60 M-T0 control, peel adhesion results with DS 40:60 M T-1 did not appear to change, but a steep decrease was observed for DS 40:60 M-T2 to M-T4, conceptually demonstrating that surface topography impacts the adhesion of TDS products.

The same TDS product when attached to stainless steel required higher force to peel, compared to the DS substrates. This indicates that apart from topography, surface chemistry and physical properties of the substrates can also influence TDS adhesion results.

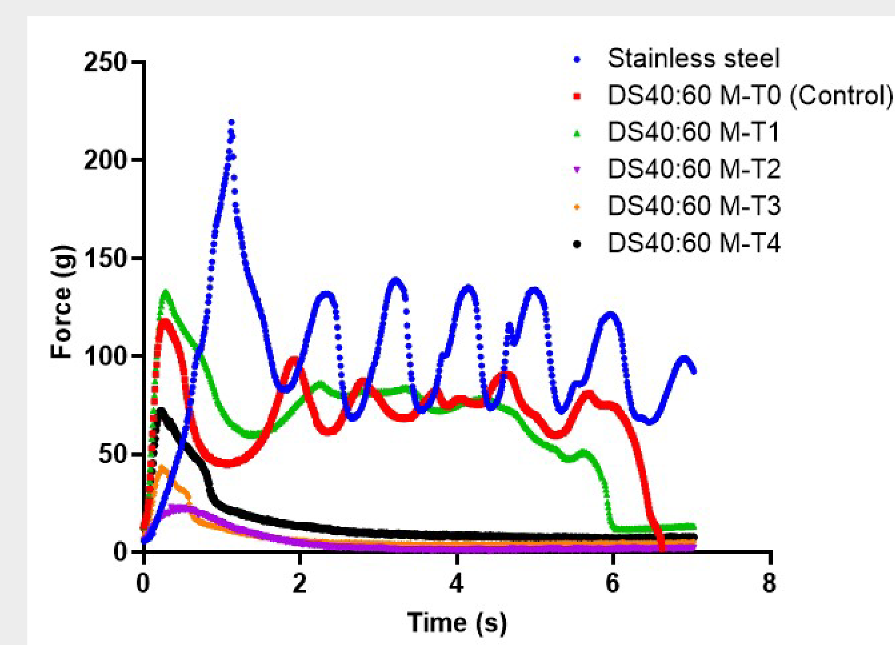


Figure 4. Mean peel adhesion profiles of an over the counter (OTC) TDS product (NicoDerm) on stainless steel and on 5 developed DS 40:60 substrates incorporated with topographical levels (M-T0 to M-T4, low to high) (n=2).

CONCLUSION

- Substrate topography impacts TDS adhesion and, when designed appropriately, may be an important factor to incorporate into the development of skin-mimetic substrates for in vitro TDS adhesion testing.
- Characterization of human skin properties is underway to refine and guide the further development of bio-relevant in vitro TDS adhesion test methods.
- Such test methods have the potential to help mitigate the risk of adhesion failures, during product development and throughout the lifecycle of TDS products.

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