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Abstract

Excessive frictional loading to the skin often results in the formation of blisters, due to the transmission of shear loading to the interfaces between dermal cell strata. The consequences of blistering range from mild discomfort to serious infection. In some patients, such as those disposed to epidermolysis bullosa (EB) or neuropathic diabetes, blisters can severely degrade life quality. Investigation of environmental and application parameters that affect blister formation has occurred primarily as a qualitative, observational pursuit on human subjects, which has often led to confounding of data and lack of repeatability. The authors have developed a Synthetic Skin Simulant Platform (3SP) that reproduces the mechanical behaviour of human skin when exposed to tribological loading. The platform is an assembled construct of bonded elastomeric layers that act as surrogates for the epidermis, basement membrane, dermis, and subdermal structure. Epidermal (top layer) materials are typically silicone or polyurethane (PUR) films with a friction coefficient akin to human skin, while sublayers display mechanical properties similar to their anatomical analogues. Blistering is evident optically by examining the separation voids formed after applying shear loads to the epidermal layer. The 3SP has been used in a two-axis pin-on-flat tribometer with a stainless steel indenter to study the normal load and friction coefficients encountered at the onset of frictional blistering. The 3SP allows for modulation of friction coefficient, interfacial adhesion strength, and subdermal stiffness for investigation of blistering damage to various anatomical sites. Experimental results have been compared to human test data and have shown that the 3SP provides the potential to make significant advances with respect to skin tribology research.

1. Introduction

Human skin is the largest organ of the human body and the primary line of defense between internal organs and the outside world. Therefore, any disease or trauma that causes a breach in this protective layer threatens not just comfort, but potentially health and life, as well. Friction blisters are a very common mode of skin damage, with

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consequences ranging from mild discomfort to infection and disease. Skin is composed of multiple layers, the innermost layer being the dermis which sits upon a subcutaneous layer of adipose tissue. The outermost layer of skin, the epidermis, is composed of progressively dying and hardening cells that migrate away from the dermis before sloughing away. Epidermal layers, in the order of their distance from the dermis, include the stratums basale (newly generated cells), spinosum, granulosum, lucidum, and, finally, the corneum at the very outside surface of the epidermis. The stratum spinosum acts as the anchoring system for layers in the epidermis; therefore, when these cells are injured, they allow the formation of pockets of fluid to form between strata in the epidermis [1]. This is distinct from surface damage. When the coefficient of friction between a foreign surface and the corneum layer is sufficient, slippage ceases and shear load is transferred to the layer interfaces within the epidermis [2]. Friction blisters form under such shearing trauma when the stratum granulosum separates from the stratum basale [3]. The newly-formed pocket between these two strata then fills with fluid, leading to an inflamed bubble which becomes susceptible to further injury. Occupational blister research has been pursued for several decades, dating back to the 1950's with Naylor et al. and Sulzberger et al. performing in situ blistering tests on human test subjects [2, 4]. Subsequent blister research has focused on observation of blister formation influenced by coefficient of friction (COF) [1] and moisture effects [5] at the skin site. Research into the mechanical [6, 7] and tribological properties [8] of skin has accelerated due to the interests of tactile optimization of products, as well as the cosmetics industry.

In examining prior research of friction blisters the authors noted that, while impressively systematic, these studies tended to take an observational or biological approach to understanding blister formation. There has been little attempt to characterize blistering from an engineering perspective. Furthermore, all investigators that have worked in this field have been limited by the necessity to conduct experiments on human test subjects. Notwithstanding the ethical and legal difficulties of intentional skin injury of test subjects, there are also very significant issues of repeatability with human test subjects. Studies have shown that the behavior of human skin is highly variable from person to person [9]. As such, there is a significant need for the creation of a construct that can accurately model the behavior of human skin under shear loading. An investigation of the mechanics of skin blistering has revealed five parameters of interest that were the subject of this investigation: coefficient of friction, dermal stiffness, interlayer bond strength, normal load, and shear rate. By focusing on these central mechanical and tribological parameters of skin, the authors sought to design a synthetic surrogate system to serve as a research platform for continuing blister research.

2. Material and Methods

2.1 Platform Design and Preparation

The design of the Synthetic Skin Simulant Platform (3SP) focused on the blistering mechanism of human skin. Blisters form between layers in the epidermis when subjected to shear loading, thus attention was paid to proper selection of materials in light of the reported mechanical properties of real skin. The 3SP implemented a tri-layer design to simulate blister formation under applied shear loading. The structure of the 3SP is shown in Figure 1.

The top layer of the 3SP is referred to as the Epidermal Simulant Layer (ESL). It consisted of 0.8-mm thick transparent silicone rubber (McMaster-Carr, 40 A durometer), to simulate the stratum corneum. While this layer is much thicker than human stratum corneum, its function remains analogous: it interfaces with external stimuli and blisters under significant shear forces. Thinner layers of silicone were tested, but they were too fragile to be useful. As with human skin, the critical property of this layer is its coefficient of friction (COF). Silicone was chosen because it has been shown to approximate the COF of human skin against a number of surfaces [7]. The silicone used in the 3SP may be roughly compared to damp skin on the forearm or heel, however it was not precisely calibrated to match an exact site. The transparency of the ESL was also deemed important in order for blister area to be measured after testing, as described below. For each platform constructed, the silicone was cut into a 5 x 7.6-cm rectangle to prepare for bonding to the layer below. The Dermal Simulant Layer (DSL) consisted of a 3.18-mm thick layer of either polyurethane elastomer (McMaster-Carr, 40 OO durometer) or neoprene rubber (McMaster-Carr, 30 A durometer) cut to a 7.6-cm square. The choice of DSL material allowed for investigation of the effects of dermal stiffness on blister formation. When selecting materials for this layer, the key consideration was its response to normal loading; the authors selected the above two materials to simulate the range of stiffness found at different anatomical sites on the body, from the softness of the human hand to the stiffness of ankle or heel skin. Due to the thinness and compliance of the top two layers, the authors found that the ESL and DSL experienced significant substrate effects when they were adhered directly to the mounting substrate, thus the Subdermal Simulant Layer

(SSL) was incorporated. In the absence of the SSL, the stiffness of the 3SP was dominated by the hard mounting plate beneath them.

The SSL consisted of 3.18-mm thick latex rubber (McMaster-Carr, 35 A durometer) cut to a 7.6-cm square. Another objective of incorporating the SSL into the platform was to simulate the tendons, fat and muscles that sit between bone and the dermis in the body.

In addition to the properties of the 3SP layers, another critical parameter of the construct was the adhesive strength between the ESL and DSL, since it was the interface involved in blistering. A methyl ethyl ketone adhesive (Loctite® No. 79051333) was selected as an adhesive because it provided good adhesion between the two layers and the adhesive strength could be modulated by dilution with acetone. The ESL and DSL were bonded using the adhesive in regular or thinned (50% acetone dilution, by weight) form, to provide 'high' and 'low' values of adhesion for the factorial experiments described below. The adhesive was applied evenly to the surface of the ESL using a paint brush. Any bubbles between the ESL and DSL were manually smoothed out by hand, paying special attention to minimizing the deformation of the layers during application. A flat plate was pressed against the top of the ESL immediately after establishing contact with the DSL to produced smooth bonding across the interface. A distributed compressive load of approximately 55 N was applied for 30 minutes during adhesive curing. A silicone-based adhesive was used to join the DSL to the Subdermal Simulant Layer (SSL), as well as the SSL to the mounting substrate. This latter adhesive had much higher bond strength than the ESL-DSL interface to ensure blistering would occur at the appropriate interface. Adhesive was applied to the top of the SSL layer and the ESL-DSL construct was placed upon it. Adhesive was then applied to the mounting substrate (paper-backed acrylic plate) and the entire stacked platform was cured for 12 hours using a distributed compressive force of approximately 30 N.

2.2 Testing Procedure

A 2^{5-2} fractional factorial experiment was run initially to determine which of the five material and loading parameters had an effect on blister formation and surface damage. These parameters were: a) coefficient of friction (COF), b) dermal stiffness, c) bond strength, d) normal load, and e) shear speed. The experiments were performed with a custom-built dual-axis tribometer. The instrument facilitated precisely controlled contact between a 9.5-mm diameter stainless steel ball and a 3SP sample under a controlled normal load. The ball was reciprocated linearly across the exposed ESL portion of the 3SP surface with a round-trip travel length of 60 mm per cycle, for 100 cycles. COF of the Epidermal Simulant Layer (ESL) was set to 'low' and 'high' values by the presence or absence, respectively, of a thin layer of corn starch on the exposed ESL surface just prior to testing. This produced measured COF values of the ESL of 0.23 and 0.71, respectively. 'Low' and 'high' normal loads of 3 and 9 N, respectively, were chosen to coincide with prior blister research on human subjects performed by other investigators [2]. Normal load was controlled using a pneumatic actuator with analog regulator, with precise values monitored by a three-channel piezo-electric force transducer (Kistler) that was positioned between the stainless stell ball probe and the actuator piston. The transducer output was recorded using data acquisition hardware and software and COF was measured by calculating the ratio of shear force to normal force. The test settings for the experiment are outlined in Table 1.

Two response variables were identified for the tested 3SP samples: blister area and surface damage. Blister area was determined by using image analysis software (ImageJ) to detect the debonded (blistered) area of a tested 3SP sample. A grayscale threshold technique was implemented in the software to automatically detect the blister boundaries through the transparent silicone ESL layer. Surface damage, being very difficult to objectively measure, was instead characterized on a 1 through 5 ordinal scale. These two measures, blister area and surface damage, allowed the investigators to determine damage both to the substrate and the surface. Each level of the surface damage scale is explained below in Table 2.

Based upon an analysis of the data produced by the fractional factorial experiment, a second experiment with newly-constructed 3SP constructs was conducted with the 3SP samples under a 2^3 full factorial plan, with focus on three of the original parameters that showed potential effects on blistering and surface damage: surface treatment, dermal stiffness, and shear speed. The other two parameters, normal load and bond strength, were held constant at 6 N and undiluted adhesive strength, respectively. Blister area and surface damage were recorded in the manner described above.

3. Results and Discussion

Observation of the testing revealed that a similar pattern of events occurred among all the 3SP samples that experienced blistering. During the initial abrasion cycles, the sample showed little damage, although there was often a noticeable surface disturbance along the leading edge of the stainless steel probe. This disturbance appeared to reflect the 'bow wave effect' observed during human in situ tests by Kwiatkowska et al. [10]. When the probe moved along the 3SP, the material compresses ahead of it, causing an elevated wave ahead of the indenter and leaving behind a distended wake. Although not all samples blistered, in the samples that did, the onset of blistering at the ESL-DSL interface occurred following an initial period of bow wave production. The early blister first took on the shape of a sharp oval, with its major axis perpendicular to the rubbing direction, which elongated in the direction parallel to motion as it grew. In the case of several samples, blistering occurred at multiple points along the wear path and coalesced into oblong blisters oriented parallel to the direction of motion.

Examination of tested samples, as illustrated in Figure 2, showed varying extents of blister area and surface damage based on the sample and test conditions. The black areas represent ESL-DSL bonding that has been maintained (non-blistered). The gray regions show where the ESL has lifted from the DSL, representing a blister. Not all tests produced blisters and/or surface damage, but Fig. 2 shows significant damage for each run. Surface damage caused an increase in opacity of the silicone ESL layer, which was helpful in characterizing how damaged the surface had become. Table 4 is provided to indicate the results for the various test configurations of the fractional factorial experiment.

An analysis of variance (ANOVA) of blister areas from the first factorial experiment is reported in Table 5. The table shows that of the five parameters, dermal stiffness and shear speed have a clear effect on blistering, surface treatment appears marginally involved, while changes in bond strength and normal load within the bounds of the experiment had no measurable effect. A non-parametric analysis of the surface damage medians yielded similar conclusions. Modification of surface treatment led to a change in surface damage median of 1.5, while varying dermal stiffness led to a damage median change of 3. Variation of none of the other factors led to this high of a magnitude of median change, and so were assumed not to have a measurable effect on surface damage. The fractionation of the first experiment led to potential confounding of main effects with some of the possible interactions, so based on the results of the ANOVA, the second experiment was run as a full factorial to further investigate surface treatment, dermal stiffness, and shear speed, as well as any possible interactions among them.

The relative insignificance of normal load and bond strength was unexpected. Prior work by Naylor et al. suggests that blistering depends directly on load and number of cycles [2]. This discrepancy may be due to the loading values tested by the authors. Neither Naylor nor Sulzberger [4] monitored normal load in situ during their testing, but rather recorded applied load in the form of set weights. This suggests that method of normal load application must be further investigated as this work continues.

Analysis of variance of the second experiment allowed for both main effects and interactions to be resolved. ANOVA revealed that dermal stiffness (p-value of <0.001), surface treatment (<0.001), and the stiffness-shear speed interaction (<0.001) did have an effect on blister area. Interestingly, shear speed did not have an effect on blister area in the second experiment (p-value 0.837), contrary to the first experiment. This may indicate potential confounding of shear speed with a multi-factor interaction in the first experiment that was not detected due to the limitation of the fractional factorial design. Specifically, there is a possibility that there was an interaction between shear speed and normal load in the first experiment. The reasoning for this is that the second experiment held normal load constant (6 N) while it was varied between two values in the first experiment (3 and 9 N, respectively). Naylor found no correlation between shear speed and blister formation at similar COF values [2]. These results may suggest the effects of viscoelasticity of the materials such that the 3SP (and actual skin) behaves more rigidly at high shear speeds. Kwiatkowska suggested that the strain energy of the material is more easily lost at high sliding speeds[10], so the effect of shear speed may be confounded by the dermal stiffness. The bow wave was particularly prominent in PUR samples. Further investigation will be required to determine the precise effect of shear speed and under what conditions it affects blistering potential. Another important issue that was beyond the scope of this work, is the effect of layer thickness on blister formation. This is vital with respect to observations that blistering can only occur in particular anatomical locations that have a sufficiently thick epidermis. The 3SP approach offer the potential for future investigators to determine the thickness effect. One other point of comparison of the 3SP concept with the behavior of skin is the fact that COF, directly controlled by the surface treatment, had a profound effect on blister formation. This is in agreement with the work of Derler [7] and others [3, 5]. The ultimate objective in developing the 3SP approach is to duplicate the behavior of human skin under shear loading. The results of this study suggest that, while some improvement remains to be undertaken, the fundamental aspects of the 3SP behavior are relevant to skin.

One very intriguing result of this work that may influence future blister research, is the strong effect of dermal stiffness. Akers noted that blisters form more quickly on wet skin[3], attributing it only to the effect of hydration on friction coefficient. In a separate study, Alonso et al. found that hydration also makes skin softer [11]. The use of the 3SP constructs offers one way to connect these two findings in that the results showed dermal stiffness to be just as significant as COF. Though it is difficult to imagine current medical interventions that could easily increase dermal stiffness, this insight may inspire analogous stiffening methods to prevent blister formation. An aspect of the 3SP that may require future improvement is the fact that the true dermal/epidermal interface in skin is a complex three-dimensional interface. Such a configuration has unique mechanisms to minimize shear stress through a rudimentary mechanical 'interlocking' of the layers. The current implementation of the 3SP involves a flat-on-flat interface, but it is relatively straightforward to produce a more realistic interface through the use of castable elastomeric resins that have texturing at the intermediate interfaces. Another consideration to be made is the biological mechanisms of blister formation that happen concurrently to the mechanical processes. Inflammation and the influx of fluid at the blistering interface likely have an accelerating effect on blister growth and weakening of the epidermis. While not incorporated into the current 3SP approach, it is conceivable in future investigations to incorporate such behavior using a porous dermal simulant layer with fluid pressure applied from the substrate. Initially, the ESL/DSL bond would prevent fluid influx, but fluid would begin to flow into areas of incipient delamination (blistering).

Future development of the 3SP concept will necessitate studies on explanted skin, whether animal-derived or cadaveric. Such work will be necessary in order to choose construct layers and bonding agents that replicate dermal tissue to an even greater extent than the current work. The modular nature of the 3SP approach allows for innumerable possibilities in optimizing the platform for varying skin types, anatomical locations, and environmental factors. For example, the combination of a soft polyurethane Dermal Simulant Layer (DSL) with no surface treatment to the Epidermal Simulant Layer (ESL) may model the hydrated skin on the abdomen, while a harder neoprene DSL with a corn starch treatment on the ESL could model the dry skin of the volar forearm. The results of this investigation of the 3SP concept demonstrate significant potential for the system to become a powerful tool in future blister research for medical and commercial applications.

5. Conclusions

The authors have developed a modular, tri-layer elastomer-based experimental construct called the Synthetic Skin Simulant Platform (3SP), that allows for precise investigation of the parameters involved in frictional skin blistering. The 3SP addresses obstacles in skin tribology research regarding the use of human subjects, inability to control biological variability among subjects, and undesired coupling of various mechanical and tribological properties of skin in human subjects. The following conclusions are based on the results of this investigation:

- Blister area and surface damage of the 3SP is strongly affected by the coefficient of friction (COF) of the epidermal layer. Higher COF lead to larger blisters.
- The stiffness of the dermal simulant layer of the 3SP also had a strong affect on the area of blisters generated during the testing. Stiffer dermal materials tended to have smaller blisters than less-stiff dermal materials.
- Shear speed of the stainless steel sphere on the epidermal layer of the 3SP showed varying results based on the normal load applied. This may suggest that speed, normal load, and dermal stiffness interact during blister formation, a postulate that has been suggested by previous researchers.

References

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Tables

Table 1: Factor level settings for first fractional factorial experiment

Variable	Low Value	High Value
Surface Treatment	Corn starch	Untreated
Dermal Stiffness	40 Shore OO (PUR)	30 Shore A (neoprene)
Bond Strength	Full strength	50% diluted
Normal Load	3 N	9 N
Shear Speed	25 mm/s	50 mm/s

Table 2: Surface Damage Characterization

Damage Level	Explanation
1	No visible damage to surface
2	Shallow trough along surface of wear path
3	Waves in the trough
4	Bumps in the trough that protrude above the adjacent surface level
5	Extensive ripples with visible markings of damage and/or tearing

Table 3: Factor level Settings for the second experiment

Variable	Low Value	High Value
Surface Treatment	Corn starch	Untreated
Dermal Stiffness	40 Shore OO	30 Shore A
Shear Speed	25 mm/s	50 mm/s

Table 4: Blister and surface damage results from the first experiment. 'Low' and 'high' settings for each parameter are indicated by capital and lowercase letters, respectively. A represents surface treatment, B dermal stiffness, C bond strength, D loading, and E shear rate.

Test Configuration	**Blister Area (cm^2)**			**Surface Damage**
	$\overline{x}$	S	n	median
1 (abcDE)	1.165	1.249	6	3
2 (Abcde)	2.444	0.729	6	5
3 (aBcdE)	0.000	0.000	6	1
4 (ABcDe)	1.020	1.390	6	3
5 (abCDe)	1.865	0.749	6	5
6 (AbCdE)	1.049	0.617	6	3.5
7 (aBCde)	0.000	0.000	6	1
8 (ABCDE)	0.532	0.660	6	1.5

Table 5: First Fractional Factorial ANOVA results. * indicates effect has statistical significance at 95% confidence

Source	SS	df	MS	F	p-value	
Surf. Treatment	3.048	5	3.048	4.419	0.042	*
Dermal Stiffness	18.534	1	18.534	26.872	< 0.001	*
Bond Strength	1.049	1	1.049	1.521	0.224	
Normal Load	0.888	1	0.888	1.287	0.263	
Shear Speed	5.002	1	5.002	7.252	0.010	*
Error	28.969	42	0.690			
Total (corrected)	57.490	47				

Figures

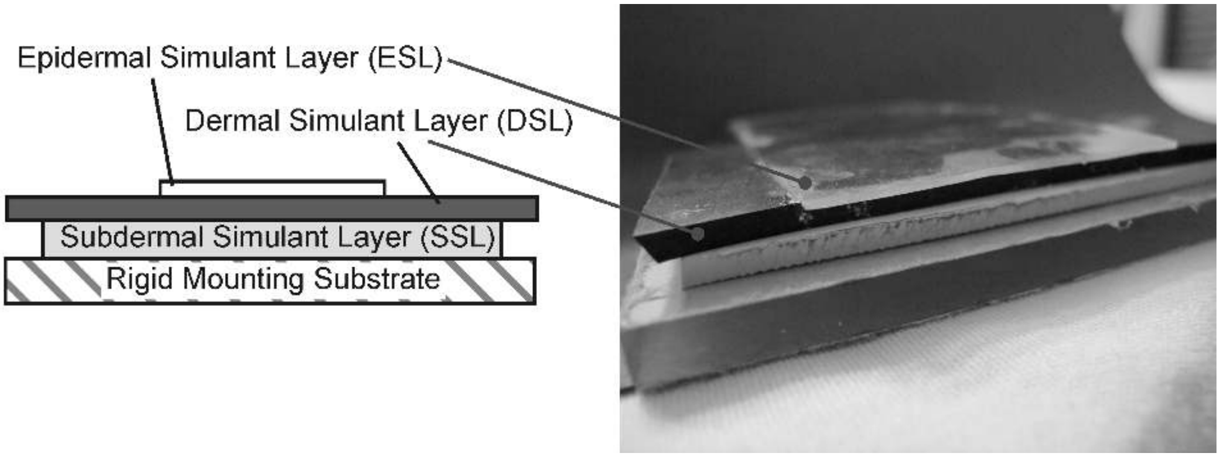

Figure 1: Illustration of the layered structure of the Synthetic Skin Simulant Platform (3SP)

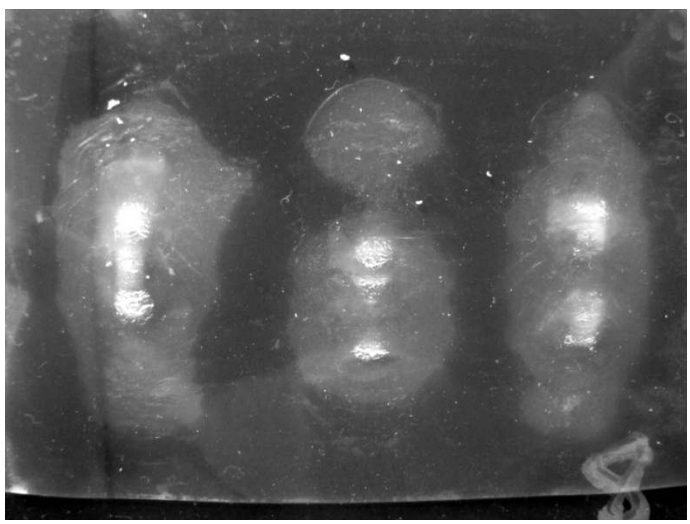

Figure 2: Results of three tests of a 3SP sample under the following conditions: no surface treatment, low dermal stiffness (polyurethane), 50 mm/s shear speed, and 6 N normal load. The light-colored regions are blisters, while the bright white regions indicated significant surface damage