CLINICAL METHODS FOR EVALUATION OF WEAR AND PAIN IN MEDICAL PRESSURE SENSITIVE ADHESIVES

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Adhesives for low trauma (easy removal) products are increasingly in demand due to significant mega trends including an aging population, an increased incidence of chronic conditions, and an expanding network of non-physician healthcare providers. Understanding what consumers define as "low trauma," and developing and implementing more robust screening methods for low trauma pressure sensitive products is key for addressing the needs of this market segment. This paper discusses the results of several clinical pain and wear trials aimed at defining/refining key criteria for low trauma products from the consumer perception. It also will review correlations between the clinical trials and lab testing methods with the goal of identifying key/critical tests for product evaluation.

There have been several literature approaches to evaluate wear and pain of medical grade pressure sensitive adhesives (PSAs). A recent paper at Tech 38 by Contrada contains many of the commonly used approaches for evaluating medical PSAs: rheological measurements and performance testing including peel from stainless steel and high density polyethylene (HDPE), probe tack and static shear. This work also included a clinical trial involving a pain rating scale of 0 to 5. The author drew a general correlation between the pain rating from the clinical trial and low adhesion as determined via the various techniques.

At Tech 35, Liu presented an overview paper on medical tapes. A unique test approach from Liu's overview was the value of Trans Epidermal Water Loss (TEWL) as a measure of skin stripping. The TEWL data was used to provide a basis for understanding one important source of pain upon adhesive removal: stripping (removal) of skin layers by the adhesive.

Lab Testing

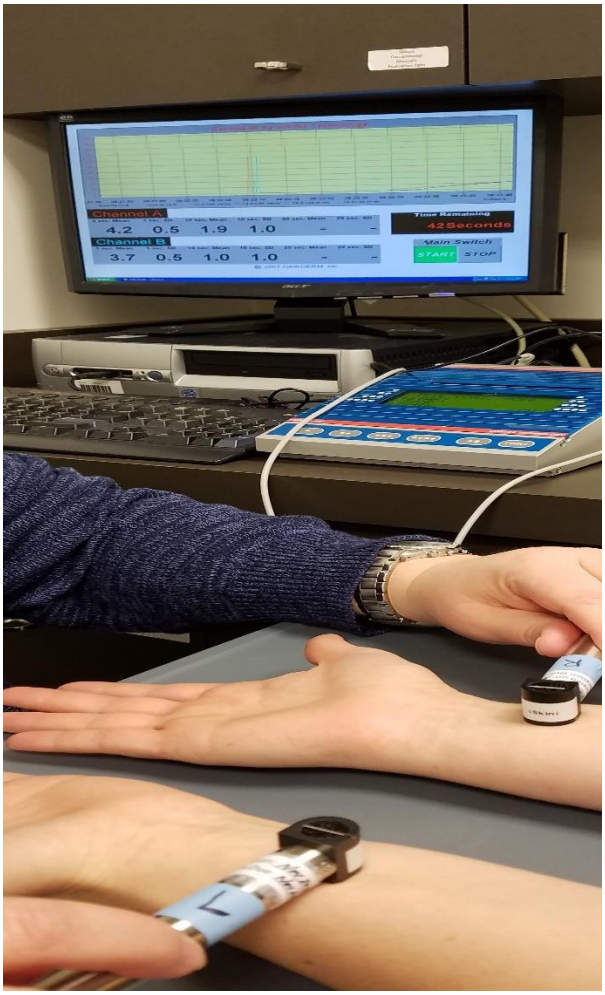
For this study, several of the historic approaches were evaluated and correlated with the results of the clinical trials.

Peel measurements were performed to provide a basis for correlating pain and wear measurements with a lab measurable screening tool. Samples were coated at a 2 mil coatweight as a free film, laminated to a 1.2 mil thickness breathable polyurethane (PU) film. Performance measurements included 24 hour peels from low density polyethylene (LDPE) and VITRO-SKIN® N19. LDPE was chosen as the polyolefin material with the closest surface energy match to human skin (closer than the high density polyethylene and polypropylene options used/referenced in other literature work). Stainless steel was not used despite literature work due to the large mismatch in surface energy versus skin. The dwell time for the performance testing was chosen to match the desired skin contact time in the clinical trials. VITRO-SKIN®[1] N19 (referred to as "VITRO-SKIN" for the remainder of this paper)

[1] VITRO-SKIN is a registered trademark of Innovative Measurement Solutions Inc.

is a synthetic skin substitute available from IMS Inc. that is formulated to have topography, pH, critical surface tension and ionic strength that is similar to human back skin.

DERMALAB® open chamber probes were used to measure the Trans Epidermal Water Loss (TEWL) values on the individuals. TEWL readings were taken on each of the six test sites at baseline and approximately 30 minutes' post removal of the test strips. The six test sites were located on the inner forearm of the subjects where TEWL readings were done in duplicate for a period of 1 minute a piece. The two one-minute reading values were then averaged for the final TEWL calculations. This noninvasive probe functions by measuring the vapor pressure gradient with two hygrosensors and thermistor sensors at differing distances from the arm. The vapor pressure gradient is then used to calculate the TEWL value. Overall, changes from baseline calculations were completed to determine skin damage/changes.



Protocol Development

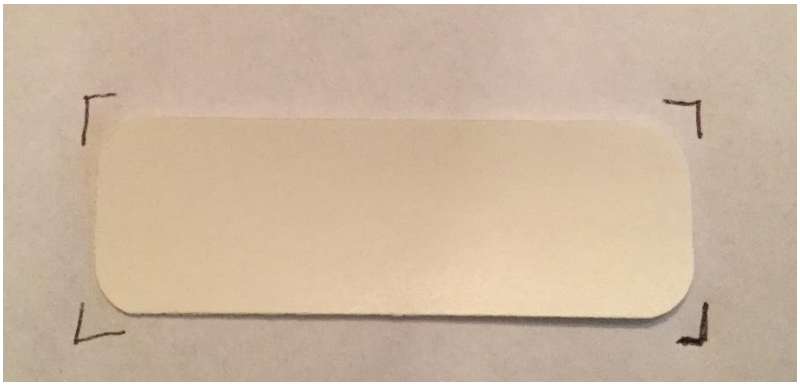
In order to design and execute a clinical trial protocol, the specific market segment(s) need to be clearly identified. Each market segment has specific requirements for the adhesive that determine the necessary parameters to be used in the clinical trial protocol.

For a clinical trial protocol, specific items that should be considered in the protocol design process:

1. Adhesive construction.
2. Test location on the human body.
3. Size of the construction to be tested.
4. Number of different samples/products to test.
5. Conditions of the clinical trial. This can range from normal patient wear, heavy exercise for a short/defined period of time, shower/bathing allowed or not allowed, etc.
6. Skin preparation: shaved/not-shaved, alcohol wipes, etc.
7. Control materials to include in the trial. In an ideal clinical trial protocol, both positive and negative controls are included. The positive control would ideally be "Best in Class" in some attribute or in the balance of all performance requirements.
8. Measurement attributes. Examples include (but are not limited to) wear (length of time and quality of adhesion), pain, and irritation
9. Number of individuals.
10. Test population for the clinical trial: male, female, specific age groups, etc..

The specific focus area covered in this paper is low trauma medical PSAs targeted for wound care. The design process used for our specific clinical trial protocol definition:

1. An adhesive construction consisting of a single coated adhesive (no interlayer) using a market grade breathable polyurethane (PU) film. The sample size was chosen to be a 1" by 3" strip. This is a simplified construction in the basic shape of a common wound care product.



2. The test area was chosen to be the lower volar (interior) portion of the arm.

2. A total of six (6) sample strips were tested on each individual.
3. Two control samples were included in the clinical trial: a high adhesion, long wear acrylic adhesive, and a low trauma silicone product.
4. After the initial "proof of concept" pilot clinical trial with both men and women, the clinical trials were conducted with adult women with no significant skin related health conditions. Women have less body hair then men, allowing for a simplified interpretation of the results (minimizing impact of body hair).
5. Clinical trial size (# of individuals) ranged from 10 to 30 individuals.
6. No effort was made to limit the activity of the tested individuals; individuals were permitted to go about their normal daily activities.
7. Skin preparation was an alcohol wipe prior to application of the test strip.
8. Tested parameters were adhesion (wear), pain upon removal, irritation both immediate and 30 minutes' post removal, adhesive transfer and TEWL. The multiple irritation measurements were performed to distinguish between short term irritation arising from the adhesive removal (physical pulling of the skin) versus "actual" irritation of the skin due to the adhesive chemical and physical characteristics. Rating scales used for clinical trials were as follows:

Wear scale for clinical trials:

Grade	Wear (Adhesion) Description
0	Test strip off
1	Test strip almost off (hanging)
2	¾ of test strip off
3	½ of test strip off
4	¼ of test strip off
5	3 to 4 edges lifted
6	1 to 2 edges lifted
7	All corners adhering firmly

Pain scale for clinical trials:

The Wong-Baker pain measurement scale used for these clinical trials is commonly employed in the medical profession.

Mass Transfer scale for the clinical trials:

Grade	Mass Transfer
0	No residue/transfer
1	Trace amount of residue/transfer
2	Thin presence of residue/transfer
3	Marked, specific amount of residue/transfer
4	Heavy amount of residue/transfer
N/A	Test strip fell off

Erythema (Irritation) scale for the clinical trials:

Grade	Erythema (Irritation)
0	None- no evidence of erythema other than natural skin tone
1	Slight – barely perceptible increase in light pink coloration – localized or diffuse
2	Mild – perceptible increase in link pink coloration, localized or diffuse
3	Moderate – diffuse pink coloration, localized or diffuse areas of reddened skin
4	Severe – intense redness, diffuse or localized

Clinical Trial Results and Lab Correlations:

Several clinical trials were conducted as part of this project. The first/pilot clinical trial involved multiple technologies: a silicone adhesive at 8 mil coat weight, two solvent acrylic products at 2 mil coat weight, two rubber based hot melts at 2 mil coat weight, and an emulsion acrylic at 2 mil coat weight. The clinical trial results are shown in Table I.

Table I: Testing Results from Clinical Trial #1

Adhesive	Pain Rating (0-10)	Mass Transfer (0-4)	Wear Rating (0-7)	Immediate Irritation (0-4)	30 Min Irritation (0-4)
Silicone (Positive Control)	1.2	0.1	5.6	0.1	0.0
Hot Melt PSA A	1.6	0.2	4.6	0.2	0.2
Solvent Acrylic PSA B	1.7	0.5	6.5	0.4	0.3
Emulsion Acrylic PSA C	1.9	0.6	6.7	0.4	0.3
Solvent Acrylic PSA D (Negative Control)	3.0	1.2	7.0	0.6	0.5
Hot Melt PSA E	0.2	0.0	0.8	0.1	0.1

Conclusions from this clinical trial included:

1. Even with an aggressive solvent acrylic (PSA D), the pain rating is relatively low on the scale used.
2. Mass transfer showed very minor amounts of adhesive transfer/residual adhesive on skin.
3. Wear ratings for the acrylic products (solvent and emulsion) are quite good in this specific construction and time duration.
4. Erythema (irritation) is quite low and independent of the adhesive. There is also little change in irritation between immediate and 30 minutes' posttest strip removal.

For the second clinical trial, TEWL measurements were also included.

Table II: Testing Results from Clinical Trial #2

Adhesive	Wong Baker Pain Rating (0-10)	Mass Transfer (0-4)	Wear Rating (0-7)	Immediate Irritation (0-4)	30 Min Irritation (0-4)	TEWL
Solvent Acrylic PSA F	3.7	0.8	7.0	1.0	0.8	4.3
Solvent Acrylic PSA D (Negative Control)	3.4	0.8	7.0	0.6	0.5	2.1

The key result from this clinical trial showed that TEWL shows are a marked difference between PSA F and PSA D. These two adhesives show equivalent 24 hour wear and pain ratings, yet PSA F shows significantly higher change in TEWL values. This approach has the potential to differentiate products for suitability for repeat usage applications via differentiation of skin layer stripping potential of differing adhesives.

Based on the clinical trials, data analysis was conducted in several ways to (1) correlate the results to lab measurable tests, and (2) understand the strengths and limitations of the clinical trial protocol approach used for this work.

In order to understand the clinical trial protocol data strengths and limitations, an analysis of the positive and negative control results across all three clinical trials was performed. That comparison is shown below in Table III for the silicone and for solvent acrylic PSA D (the positive and negative controls used in all three clinical trials).

Table III: Comparison of Positive and Negative Controls across all Clinical Trials

CT1 = Clinical Trial 1, CT2 = Clinical Trial 2, CT3 = Clinical Trial 3

Adhesive	Wong Baker Pain Rating (0-10)	Mass Transfer (0-4)	Wear Rating (0-7)	Immediate Irritation (0-4)	30 Min Irritation (0-4)
Silicone (Positive Control), CT1	1.2	0.1	5.6	0.1	0.0
Silicone (Positive Control), CT2	0.8	0.0	5.7	0.4	0.1
Silicone (Positive Control), CT3	0.7	0.1	5.1	0.1	0.0
Solvent Acrylic PSA D (Negative Control), CT1	3.0	1.2	7.0	0.6	0.5
Solvent Acrylic PSA D (Negative Control), CT2	3.4	0.8	7.0	0.6	0.5
Solvent Acrylic PSA D (Negative Control), CT3	1.9	0.5	6.9	0.5	0.1

Based on these results, the value of having positive and negative controls becomes clear. There is trial-to-trial variation on the pain and wear ratings of the control samples. This likely arises from a variety of factors including the specific individuals used in each clinical trial and the time of year (average temperature, average humidity). The last clinical trial (CT3) showed the largest delta on pain and wear for the positive control versus the other two clinical trials.

A key point from this comparison: pain ratings can only be compared within a clinical trial and not between clinical trials. The variation in the negative control between the 1st and 2nd clinical trials as contrasted with the pain rating on the 3rd clinical trial is indicative of the limitations of comparing absolute pain ratings across different trials.

It is also clear that, in general, there is little difference in erythema values between the initial and 30 minute post removal measurements.

There was some overlap of tested individuals between clinical trials (individuals participated in more than one trial). Reviewing the crossover of the same individuals across the clinical trials in Table IV and Table V (pain ratings) and Tables VI and VII (wear ratings), we see that there definitely is differences between the clinical trials even with the same individuals.

Table IV: Pain rating comparison for the Positive Control

Subject	CT1	CT2	CT3
#1	2		0
#2	.	1	.
#3	0		0
#4	2	0	
#5	2		0
#6		0	1
#7		0	1
#8		1	0
Avg.	1.5	0.4	0.3

Table V: Pain rating comparison for the Negative Control

Subject	CT1	CT2	CT3
#1	4		2
#2	2	3	0
#3	2		0
#4	1	4	
#5	3		2
#6		0	1
#7		2	2
#8		4	2
Avg.	2.4	2.6	1.3

Table VI: Wear rating comparison for the Positive Control

Subject	CT1	CT2	CT3
#1	7		7
#2	7	6	0
#3	7		7
#4	7	7	
#5	7		3
#6		6	7
#7		7	6
#8		7	6
Avg.	7.0	6.6	5.1

Table VII: Wear rating comparison for the Negative Control

Subject	CT1	CT2	CT3
#1	7		7
#2	7	7	7
#3	7		7
#4	7	7	
#5	7		7
#6		7	7
#7		7	6
#8		7	7
Avg.	7.0	7.0	6.9

Correlation of Wear and Pain Ratings to Mechanical Properties:

After completing the clinical trials, the next step was to correlate the pain and wear ratings to performance properties. The goal is to develop a lab testing approach that predicts, with reasonable accuracy, the results of clinical trials.

Figures 1 and 2 illustrate the peel results from VITRO-SKIN and LDPE as compared to the wear ratings based on the data from clinical trial #1. There is not a good correlation in either situation. Due to shifts on results between different clinical trials, no data correlation was conducted "across" trials; all plots are based on data from a single clinical trial.

Figure 1: Wear Rating vs. VITRO-SKIN 24 Hour Peel

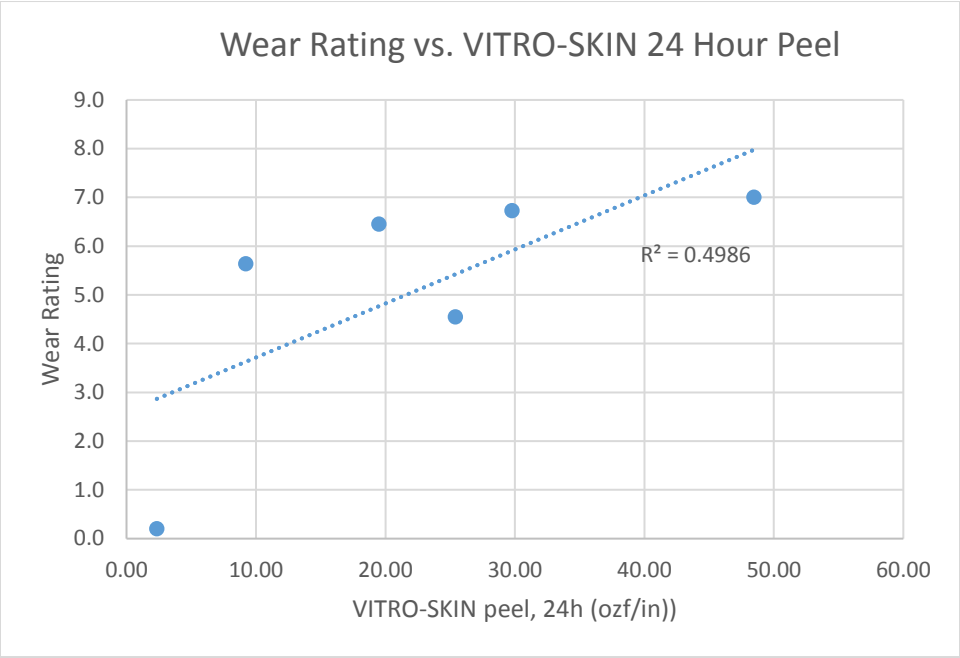
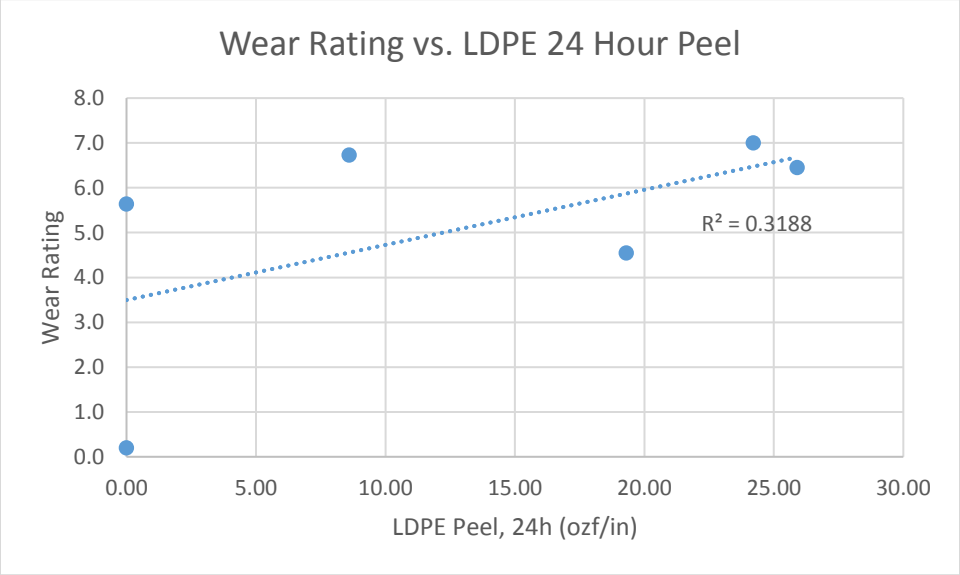


Figure 2: Wear Rating as function of LDPE 24 Hour Peel



Figures 3 and 4 show the pain ratings as a function of VITRO-SKIN 24 hour peel and LDPE 24 hour peel. There is an excellent correlation between the VITRO-SKIN 24 hour peel values and the pain ratings. Based on this results, VITRO-SKIN peel can be used as a predictor of pain upon adhesive removal

Figure 3: Pain rating as function of VITRO-SKIN 24 Hour Peel.

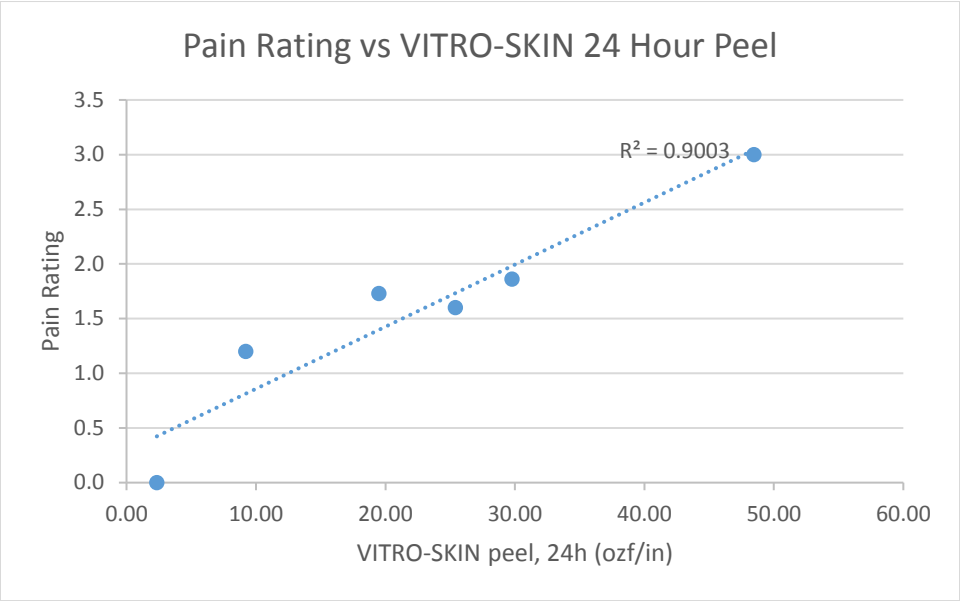
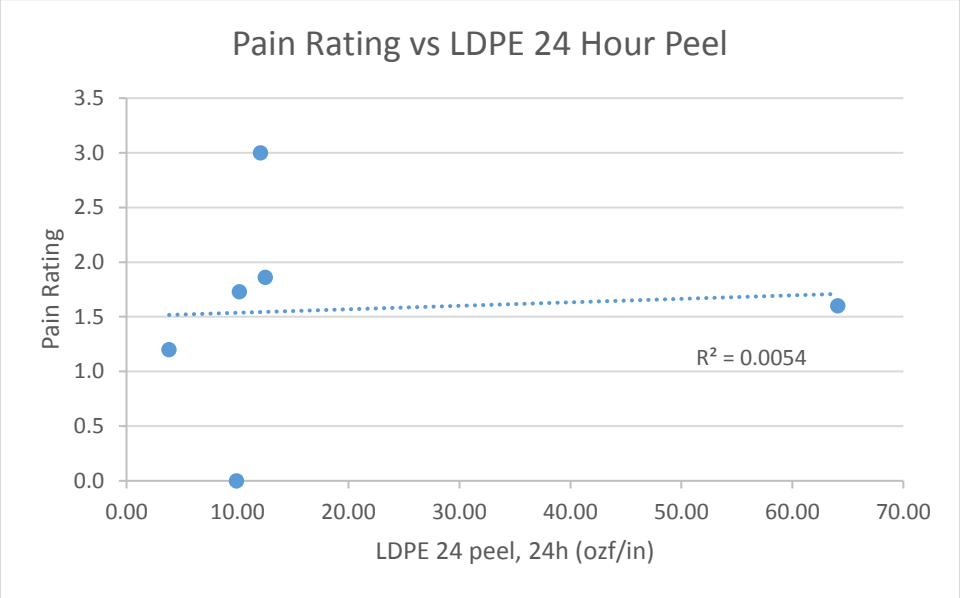


Figure 4: Pain rating as function of LDPE 24 Hour Peel



Conclusions:

This paper lays out a design input approach for clinical trials for evaluating the usage of PSAs in skin contact medical applications. The usage of the design input approach for a low trauma medical application is illustrated and applied to several clinical trials. A detailed analysis of the results from this clinical trials and peel testing is reviewed. Pain rating after 24 hours on skin was shown to correlate with peel measurements from VITRO-SKIN, a synthetic skin substrate.

References

1. “Adhesive for Gentle Removal from Skin”, S. Contrada, Berry Plastics, Pressure Sensitive Tape Council Tech 38 presentation, 2015
2. “Medical Adhesives and Skin Adhesion”, J. Liu, 3M, Pressure Sensitive Tape Council Tech 35 presentation, 2012