Pressure Sensitive Adhesive Properties as Predictors of Wear in Transdermal Drug Delivery Systems

Abstract

Human wear properties of drug-in-adhesive multi-polymer transdermal drug delivery systems can be directly correlated to the adhesive physical and chemical properties. The choice of pressure sensitive adhesive, as predicted by the monomeric composition, active residual moieties, and molecular weight will significantly influence human wear properties and water resistance.

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BACKGROUND

During the development of Transdermal Drug Delivery Systems (TDDSs) the formulator has at their disposal a variety of Pressure Sensitive Adhesives (PSAs) from which to choose. These PSAs can be either “neat” or “blend” in nature. Regardless of the nature of the PSA, its chemical composition, functionality, and molecular weight are features which directly influence the physical and chemical properties of the TDDS. Furthermore, such properties have a direct correlation to human wear and delivery of the drug(s) from the TDDS for the intended duration of use.

TRANSDERMAL DRUG DELIVERY SYSTEM PSAs

PSAs used in TDDSs are usually referred to as either “neat” or “blend” type. Neat type PSA’s can be categorized as acrylic, copolymer, and silicone. Blend type PSAs are formulated compositions normally comprising of rubber(s), elastometric polymer(s), tackifier resin(s), plasticizer(s), polymer(s), and additives. Both types can be utilized singularly, or in any combination with each other.

Whether a neat or blend type PSA is utilized in the TDDS, all posses an inherent moiety (i.e. functionality) that refers it to be either carboxy, hydroxy, or neutral and possibly a combination.

Another feature the two types of PSAs exhibit is a wide range of molecular weights. For neat type PSAs this may be accomplished either during the polymerization process and by the choice of monomers used or by the addition of a crosslinker. Blend type PSA molecular weight will most likely be varied by the choice of rubber(s) and/or elastometric polymer(s) used in their composition.

Finally, the choice of the PSA must also consider factors outside the scope of whether the TDDS will wear for its intended period. These factors include stability, solubility, component compatibility, solvent compatibility, and drug compatibility within the TDDS matrix during processing and end product storage. The incorporation of all these factors and the iterative process of planning, executing, and interpreting data utilizing both empirical and theoretical methodology is known as experimental design.
TRANSDERMAL DRUG DELIVERY SYSTEM MATRIX

Additional components, along with the neat and/or blend PSAs, are utilized in the formulating of the TDDS matrix. This may be simply the addition of a drug(s) or the addition of a myriad of other chemical structures which modify the TDDS matrix to enhance wear, chemical stability, and drug delivery. As with the TDDS PSAs, these chemical entities must be chosen with the same consideration as are the PSAs during the experimental design of the TDDS matrix.

For the remainder of this discussion, the TDDS matrix will be that which is known as a "drug-in-adhesive TDDS." This system is comprised of a backing, a drug adhesive layer, and a release liner which is disposed of prior to the application of the TDDS (i.e. peel, shear, wear, and in-vitro flux studies). Illustration 1 below is a simplified drawing of the aforementioned TDDS.

Illustration 1: Drug-in-Adhesive transdermal system

EXPERIMENTAL DESIGN

The objective set out for this experimental design was to compare three drugs-in-adhesive TDDS matrices utilizing various PSAs and components for the following:

i) in-vitro drug delivery properties
ii) peel properties
iii) shear properties
iv) wear properties

Once the data was collected, discussion of results and conclusions would then be made for each TDDS tested. The desirable and less desirable attributes of the TDDSs would be identified and recommendations would be made for improvement.
Formulation Parameters

Each of the three TDDSs were formulated with the intent that they have pressure sensitive adhesive properties, homogeneous matrices, and complete solubility of the drug at a maximum loading (i.e. subsupersaturation). Furthermore, in consideration of the drug loading, the formulations were made in the active (i.e. drug included) matrix initially to study in-vitro drug delivery properties for product viability before the placebo (i.e. drug removed) matrix was made for physical property testing.

The in-vitro drug delivery would also dictate the size of the placebo matrix to be die-cut for wear studies between the three TDDSs. The size would be based on the average in-vitro flux of the common drug amongst the three active matrices, 17-β Estradiol.

Examples

The formulation examples utilized for the scope of the experimental design were based in part of formula disclosures in United States Patents by Sablotsky and Miranda. These patents deal with the use of neat and blend PSA’s for multipolymer TDDSs, regulation of drug delivery, and solubility parameters in multipolymer TDDSs. Each of the three examples were formulated to best exemplify the patents and show the variability of physical property testing results.

All examples were prepared as wet blends using the hydrocarbon solvents which were part of the commercially available neat and blend PSAs. Additional solvents were also added for ease of blending and coating.

Active and placebo laminates were prepared by wet gap coating the TDDS blends onto a release liner, oven drying to remove the volatile solvent, and laminating the dried matrix to a backing. All active and placebo laminates had a dry weight between 10 mg/cm² and 11 mg/cm². Samples of the active and placebo laminates were then cut into their appropriate shape and size for each test.

Active/Placebo Example 1

Utilizing the teaching for formulations of a multipolymer TDDS as described by Sablotsky, a cross-linking carboxy functional copolymer PSA was chosen as the backbone for this example. The PSA properties of the adhesive were further modified by the addition of a blend PSA, a elastometric polymer, a thermoplastic polymer, various plasticizing agents to modify tack, a colloidal clay to increase cohesivity, and finally the drug. The matrix laminate was found to have adequate PSA properties to the touch when laminated to the backing material.

Placebo laminates were prepared utilizing the same component ratios for use in physical testing (i.e. peel and shear) and wear.
Active/Placebo Example 2

The formulation comprising this example was based on the teachings of Sablotsky(1) and Miranda(3)(4) where the blend PSA and elastometric polymer were replaced by the use of silicone PSA. The silicone PSA was blended with a non-cross-linked hydroxy functional copolymer PSA along with a thermoplastic resin, plasticizers, and drug. The active matrix laminate was found to have more than adequate PSA properties to the touch when laminated to the backing material.

Placebo laminates were prepared accordingly as in Example 1.

Active/Placebo Example 3

The active matrix for this example is a further embellishment of Example 3 because of its simplicity and PSA properties. Minor changes were made in the silicone PSA chosen and the use of a cross-linking hydroxy functional copolymer PSA. Furthermore, a change was made in the plasticizer to help with the solubility of the incorporation of the second drug Norethindrone Acetate.

Active and placebo laminate were prepared for further testing as in Examples 1 and 2.

Table 1 and Table 2 below list the components comprising the active and placebo matrices for the examples discussed above.

Table 1: Active Matrix Example Components

<table>
<thead>
<tr>
<th>Component</th>
<th>Example 1</th>
<th>Example 2</th>
<th>Example 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Neat</td>
<td>• Copolymer COOH, XL</td>
<td>• Copolymer OH, unXL</td>
<td>• Copolymer OH, XL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Silicone 60% Resin, 40% Polymer</td>
<td>• Silicone 55% Resin, 45% Polymer</td>
</tr>
<tr>
<td>PSA Blend</td>
<td>• A-B-A Rubber</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elastometric</td>
<td>• Polyisobutylene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thermoplastic</td>
<td>• Ethylene Vinyl Acetate</td>
<td>• Polyvinylpyrrolidone</td>
<td>• Polyvinylpyrrolidone</td>
</tr>
<tr>
<td>Plasticizer</td>
<td>• Dihydric Alcohol</td>
<td>• Dihydric Alcohol</td>
<td>• Dihydric Alcohol</td>
</tr>
<tr>
<td></td>
<td>• Phospholipid</td>
<td>• Unsaturated Alcohol</td>
<td>• Monosaturated Fatty Acid</td>
</tr>
<tr>
<td></td>
<td>• Monosaturated Fatty Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Petroleum Oil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive</td>
<td>• Colloidal Clay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>• 17-β Estradiol</td>
<td>• 17-β Estradiol</td>
<td>• 17-β Estradiol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Norethindrone Acetate</td>
</tr>
</tbody>
</table>
Table 2: Placebo Matrix Example Components

<table>
<thead>
<tr>
<th>Component</th>
<th>Example 1</th>
<th>Example 2</th>
<th>Example 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA Neat</td>
<td>• Copolymer COOH, XL</td>
<td>• Copolymer OH, unXL</td>
<td>• Copolymer OH, XL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Silicone 60% Resin, 40% Polymer</td>
<td>• Silicone 55% Resin, 45% Polymer</td>
</tr>
<tr>
<td>PSA Blend</td>
<td>• A-B-A Rubber</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elastometric</td>
<td>• Polyisobutylene</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thermoplastic</td>
<td>• Ethylene Vinyl Acetate</td>
<td>• Polyvinylpyrrolidone</td>
<td>• Polyvinylpyrrolidone</td>
</tr>
<tr>
<td>Plasticizer</td>
<td>• Dihydric Alcohol</td>
<td>• Dihydric Alcohol</td>
<td>• Dihydric Alcohol</td>
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<tr>
<td></td>
<td>• Phospholipid</td>
<td>• Unsaturated Alcohol</td>
<td>• Monosaturated Fatty Acid</td>
</tr>
<tr>
<td></td>
<td>• Monosaturated Fatty Acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Petroleum Oil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive</td>
<td>• Colloidal Clay</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TRANSDERMAL DRUG DELIVERY SYSTEM TESTING

In-Vitro Drug Delivery

In-vitro drug delivery testing was conducted on the active matrix examples utilizing a modified Franz Cell set-up. The sample size for each flux cell was a 0.5 cm² disc of active laminate laid on a 1.26 cm² disc of human cadaver skin. The receiver and sample volume of the saline solution for each cell is 7.5 mL. Sampling was conducted over a period of 84 hours at various intervals and the sample solution was analyzed via HPLC for the drug concentration at each interval.

A total of five samples for each of the three examples were tested and analyzed. All samples were run on the same area of skin obtained from the donor and fluxed concurrently with each other.

A graphical representation of the flux results from the three examples are shown in Figure 1 below. The in-vitro drug delivery results are plotted to show the average concentration of drug delivered over the 84 hour period.
FIGURE 1: In-Vitro Flux Data for Active Matrix Examples
Samples Fluxed @ 32.2°C; n=5

Based on the results of the flux study, the following interpretations were made:

i) Example 1 comprised of the multipolymer TDDS matrix appears to have the lowest driving force for the delivery of the drug, 17-β Estradiol.

ii) Example 2 comprised of the multipolymer TTDS matrix utilizing a silicone PSA had the highest delivery rate for the drug 17-β Estradiol.

iii) Example 3 which was similar to Example 2 had adequate delivery of both drugs incorporated into its matrix.

Finally, basing the delivery of 17-β Estradiol from each example to be approximately 50 μg/day, size ratios (of 2.9, 1, and 1.8) were determined between Examples 1, 2, and 3. The ratios between the examples implied placebo matrix sizes of 14.5 cm², 5 cm², and 9 cm² respectively to be die cut for the wear study.
Placebo Matrix Peel Testing

Peel testing of the placebo matrices were conducted utilizing Test Method PSTC-2, Peel Adhesion for Single Coated Pressure Sensitive Tapes at 90° Angle(5). Five samples of each example were tested at one day and 28 days after the lamination of the placebo matrix to the backing. Samples were stored at room temperature (22.2°C) between testing intervals. The sample size for testing purposes was 1.27 cm in width and 7.5 cm in length. The test surface was 304 stainless steel and the dwell time after application of the sample to the surface was 0.5 hours.

A plot of the peel results, reported in grams per 1.27 cm, is presented below in Figure 2.

Although all the examples exhibited PSA properties to the touch during the formulation of the active matrix examples, the peel results would indicate that Example 1 lacked the desired wet-out for peel adhesion. Examples 2 and 3 on the other hand had more than significant peel adhesion, greater than 500 gram, which may be needed for wear properties.


**Placebo Matrix Shear Testing**

Shear testing of the placebo matrices were conducted utilizing Test Method PSTC-7, Holding Power of Pressure Sensitive Tape\(^{(5)}\). Five samples of each example were tested at various intervals over the course of 28 days after the lamination of the placebo matrix to the backing. Sample were stored at room temperature (22.2°C) and 40°C between the testing intervals. The sample size for testing purposes was 1.9 cm in width and 1.27 cm in length for coverage on the 304 stainless steel panel. The sample was allowed to dwell for 0.5 hours on the panel at 32.2°C in the incubator shear chamber before the load of 500 grams was applied.

A plot of the shear results, reported in minutes, is presented below in Figure 3.

![Figure 3: Shear Data for Placebo Matrix Examples](image)

All the examples exhibited low shear, less than 100 minutes, for both the room temperature and heat aged samples. Examples 1 and 3, which used the crosslinked neat PSA, did not have a sharp increase in shear over the course of testing for the heat aged samples. This would indicate compositional stability over time for the TDDSs.
Placebo Matrix Wear Study

Based on the sample size dictated by the results of the in-vitro flux study, a wear study was conducted at Noven Pharmaceuticals, Inc. 50 volunteers were asked to wear the placebo matrix examples for a period of 84 hours and report back with their results of how each the examples wore.

The placebo matrix for each example was die-cut into a circular shape and will now be defined as “patches” for the remainder of this discussion. The patches were allowed to stand at room temperature in pouched material for approximately 3 months before the wear study. This “stand time” is allowed for complete equilibrium to occur within the placebo matrix before wear on human skin.

The volunteers were notified prior to the application of the patch to use the lower abdomen area for patch wear and to have clean, dry skin (i.e. non-moisturized) before wear.

Finally, the patches were tested for peel and shear properties prior to the wear study to confirm that no aberrations had occurred during the three month storage. The peel testing required slight modifications in that the sample length was not at 7.5 cm, but at 4 cm, 2 cm, and 3 cm for Examples 1 through 3 respectively.

The results of the wear study testing are tabulated in Table 3 below. Once again, peel results are in grams, shear results are in minutes, and wear is listed as a percentage failure (i.e. fall offs) compared to the total population, (n =50).

<table>
<thead>
<tr>
<th>Sample</th>
<th>Peel (grams/1.27 cm)</th>
<th>Shear (minutes)</th>
<th>Wear (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 1</td>
<td>14.5 cm²</td>
<td>288.2</td>
<td>10.3</td>
</tr>
<tr>
<td>Example 2</td>
<td>5.0 cm²</td>
<td>508.7</td>
<td>35.5</td>
</tr>
<tr>
<td>Example 3</td>
<td>9.0 cm²</td>
<td>731.5</td>
<td>25.3</td>
</tr>
</tbody>
</table>

From the results obtained from the wear study, it would appear that the matrices were fairly stable over the course of the three month storage for their physical properties when compared to the results of Figures 2 and 3. Although there was a shift upward in the shear results, the peel results coincide quite well to the initial peel values. Overall, the wear results coincided with the peel data much more than the shear data.
DISCUSSION OF RESULTS

The PSAs chosen for each of the examples varied in functionality and molecular weights. Although each sufficiently held up over time physically, the nature of each had limiting factors.

Example 1, which used the crosslinked carboxy functional copolymer PSA had generally good PSA properties, yet had low peel and obviously high solubility for the drug. Apparently, even the loading of the matrix with the various plasticizers could not overcome the stiffness of the neat and blend PSAs. Furthermore, the low shear and peel results were most likely caused by the plasticizer loading which would interfere with surface bonding and possibly disrupt the internal cohesive strength of the matrix.

The wear percentage for this example was also low, most likely due impart to the aforementioned reasons. Without changing the components in the example, it has been shown by Mantelle(6) that the choice of the colloidal clay may be sufficient enough to overcome the failure rate in wear.

Example 2, which used a blend of non-crosslinked hydroxy functional copolymer PSA and a silicone PSA, had good physical properties and wear properties. Furthermore, the in-vitro drug delivery was excellent. The blend of the two neat PSAs were much more effective than the complexity of components utilized in Example 1. The wear characteristics would probably be increased in this matrix by only shifting the ratio between the resin and polymer used in the silicone PSA.

Example 3, which was very similar to Example 2, exhibited all the properties which would be sought for a TDDS. The change from a non-crosslinked PSA to a crosslinked PSA coupled with the resin/polymer ratio of the silicone PSA lead to high peel (wet-out), low shear (cohesive strength), and a high wear percentage. The in-vitro drug delivery results also showed low drug solubility and a high thermodynamic driving force.

CONCLUSION

During the course of the experimental design, peel and shear properties have been assessed as predictors of human wear over an 84 hours period. Although the wear population was limited in size, the data would indicate that peel greater than 500 gram/1.27 cm coupled with shear less than 100 minutes, will yield the most predictable wear properties. Furthermore, the choice of Pressure Sensitive Adhesives have a direct impact upon the properties as indicated by the results.

Future investigations are to focus on testing the limits of the upper and lower boundaries for peel and shear values on various Transdermal Drug Delivery Systems. Such testing would help establish a reproducible “working window” for physical testing parameters to better predict human wear.
REFERENCES