An Examination of Transdermal Drug Delivery Using a Model Polyisobutylene Pressure Sensitive Adhesive

Scott Russell Trenor

Project report submitted to the Faculty of the
Virginia Polytechnic Institute and State University
In partial fulfillment of the degree of

Master of Engineering
In
Materials Science and Engineering

Approved:
Dr. Brian J. Love, Chairman
Dr. Ronald G. Kander
Dr. Sean G. Corcoran

September 11th, 2001
Blacksburg, Virginia

KEYWORDS: Transdermal drug delivery, surfactant plasticization, peel testing

An Examination of Transdermal Drug Delivery Using a Model Polyisobutylene Pressure Sensitive Adhesive

Scott R. Trenor

Committee Chairman: Brian J. Love

Materials Science and Engineering

Abstract

This work was performed as a preliminary transdermal drug delivery (TDD) study to investigate the diffusion characteristics and effects of skin surfactants *in vitro* of four active ingredients on a poly(dimethyl siloxane) polycarbonate copolymer membrane. A Franz-type diffusion cell and various receptor solutions were used. The adhesive used was comprised of a polyisobutylene-based pressure sensitive adhesive manufactured by Adhesives Research Inc. High performance liquid chromatography was used to analyze the diffusion characteristics of these systems. In addition, the effects of two skin surfactants (sodium lauryl sulfate and dimethyl sulfoxide) on the adhesive were also investigated. Results from peel testing and thermal analysis showed that the peel strength, glass transition, and softening temperature of the adhesive was greatly reduced with the addition of the surfactants.

Acknowledgements

I would like to thank the following people and organizations for their help and guidance in conducting this study and preparing this dissertation:

Dr. Brian J. Love, chairman of my committee, for offering me an opportunity to achieve this degree, invaluable discussions and insight.

Dr. R. Kander and Dr. S. Corcoran for serving on my graduate advisory committee, answering my questions and taking valuable time to review my work.

Dr. C. Thatcher and Dr. J. Fisher for insight into useful drug delivery systems.

Julie Martin for taking valuable time to review and proof read my work.

Mrs. Susette Sowers for her quick attendance to my problems with school forms.

Dr. Love's research group, specifically: Allison Suggs, Sumitra Subrahmanyan, Dan Esterly, David Brooks, and Patricia Dolez.

Optical Sciences and Engineering Research Center and Carilion Health Systems for funding this research.

The Center for Adhesives and Sealant Science, for their allowing me to attend several Adhesion Society conferences.

Table of Contents

Table of Figures

List of Tables

Chapter 1. Introduction

The first transdermal drug delivery (TDD) system, Transderm-Scop©, developed in 1980, used the drug scopolamine for the treatment of motion sickness. Although thousands of drugs could be utilized in such delivery systems, only eight drugs and 25 TDD systems have been developed to date. Current drugs utilized in TDD systems include nicotine, nitroglycerin and various hormones such as estradiol and testosterone[1,2].

There are many advantages to using TDD over more conventional delivery methods such as oral dosing. By allowing the drug to pass through the skin and into the bloodstream, the bioavailability of the drug is increased. This is accomplished by bypassing the first-pass metabolism by the liver and digestive system, allowing for smaller amounts of drug to be administered per dose. Other benefits include reduced dose frequency as well as sustained and reversible dosing, meaning that the patch can be removed to reverse any adverse side effects[1,2,3].

One major factor contributing to the small number of new transdermal systems is the difficulty in formulating compatible adhesive systems. Due to their ease of use and good stability, pressure sensitive adhesives (PSAs) are generally used medical adhesives, such as bandages and hospital tapes[1,2,4]. Medical PSAs must be biologically inert, non-irritating to the skin and cause no systemic toxicity. However, in addition to these general requirements of pressure sensitive adhesives, there are a number of other factors that must be considered when selecting an adhesive for TDD. The PSAs must also be compatible with the included drug and any excipient (a substance used as a diluent or vehicle for a drug) in order to remain stable and offer the desired solubility. In the case of TDD systems, the excipients also include skin surfactants, which may also

plasticize the adhesive. The PSA must also allow for sufficient diffusivity and permeability of any active component included. Another developmental hurdle is that the adhesive must be of acceptable regulatory status with the FDA or other regulatory commission[1,2].

For the drug to be effective, the adhesive must remain in intimate contact with the skin. This allows the drug to pass though the stratum corneum, which acts as the protective layer of the skin. The location of the stratum corneum is shown in Figure 1.1. It is because of the stratum corneum that excipients and surfactants must be added to the drug to ease the process of diffusion[1,2,3,4,5,25]. For example, most commercial hormone therapy patches such as 3M's Climara® (estradiol), Alza's Testoderm® (testosterone) and Smith Kline Beecham's Androderm® (also testosterone) all include fatty acids to enhance delivery[2]. Another study showed increases of 590% for hydrocortisone, 460% for indomethacin, 390% for ibuprofen and 340% for acitretin in transdermal diffusion through guinea pig skin when the skin was pre-treated with sodium lauryl sulfate versus no pre-treatment[6]. Dimethyl sulfoxide has also been shown to increase the rate and amount of transdermal diffusion[25]. While skin surfactants enhance diffusion, they can be detrimental to the adhesive's properties. The surfactant could reduce the peel strength or tack, which could cause premature failure of the adhesive and the removal of the patch[2,7].

Poly(isobutylene) (PIB) was the model pressure sensitive adhesive chosen for this study (chemical repeat structure of PIB is shown in Figure 1.2). Generally, PIB is synthesized by cationic polymerization in the presence of Lewis acids at -80±C. Some relevant properties of PIB are shown in Table 1.1. PIBs used as pressure sensitive adhesives are made by blending multiple molecular weights, in order to achieve the desired mechanical properties. Tackifing resins are usually added to PIB adhesives in order to add polarity and increase adhesion.

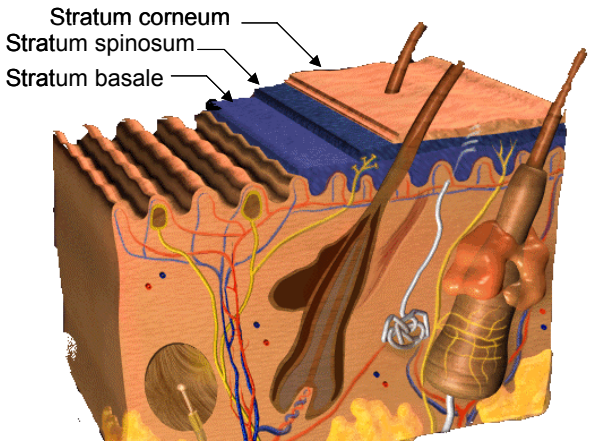


Figure 1.1 Diagram of skin cross-section.

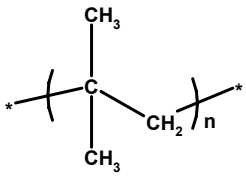


Figure 1.2 Poly(isobutylene) repeat unit.

Property	Value
Typical molecular weights[8]	500 – 6x10^6 (g mol^{-1})
Polydispersity[8]	2.0 – 4.0
Density[8]	0.917 - 0.964 (g cm^{-3})
T_g[8]	-65±C
Poisson's ratio[8]	0.49
Critical surface tension[2]	30 - 32 (mN m^{-1})

Table 1.1 Relevant properties of PIB.

One reason that PIBs are used for TDD is the polymer's critical surface tension. In order for an adhesive to wet to a substrate, the surface energy of the adhesive must be equal or less than that of the adherend. For skin, the critical surface energy varies between 38 and 56 mN m^{-1} depending on the temperature and relative humidity of the skin[2]. PIB has a critical surface tension of 30 to 32 mN m^{-1} so wetting is possible. Also, since PIBs are highly paraffinic and nonpolar, they can be used with drugs that have a low solubility parameter and low polarity[1]. Low toxicity, favorable FDA status and its light color,

making it more aesthetically pleasing, also aid in its selection for other medical grade adhesives such as surgical tape, oral bandages and ostomy appliances[9].

This project examined the use of five drugs for transdermal drug delivery: acetylsalicyclic acid (ASA), folic acid, 6-Mercaptopurine, 6-Thioguanine, and Busulfan. While there are a number of different TDD system configurations, this work focused on the drug-in-adhesive monolith shown in Figure 1.3. This system has the fewest number of components and does not include a rate-limiting barrier. The three components of the system include the impermeable backing (Figure 1.3a), the adhesive/drug/excipient mixture (Figure 1.3b) and a release liner (Figure 1.3c). The adhesive plays a number of roles in this type of system including skin adhesion, drug storage and control over delivery rate[1].

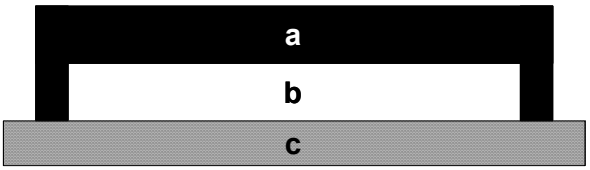


Figure 1.3 Schematic of a drug-in-adhesive monolith.

ASA, commonly known as aspirin, was chosen because it is relatively safe, well characterized and could potentially be used in a transdermal patch for continuous analgesic dosing for those with heart conditions. Folic acid was chosen due to its importance in pre-natal care and its low daily dosage requirement. Folic acid brings an added difficulty in its comparatively large size with a molecular weight of 441 g/mole. Studies have shown that the ability of active ingredients to diffuse across human skin is dependent on molecular weight, with increasing difficulty above 300g/mole and little or no passive diffusion above 400 g/mole[10,11,12,25].

Following conversations with Joan Fisher, M.D., a pediatric oncologist at Roanoke Carilion Memorial Hospital, three Chemotherapy drugs were also chosen for evaluation. 6-Thioguanine (6-TG) and 6-Mercaptopurine (6-MP) are anti-neoplastic agents used for

the treatment of leukemia. They inhibit the metabolic pathway essential for the survival of cancer cells through the inhibition of folate, purine, pyrimidine and pyrimidine nucleoside pathways required for DNA synthesis. These two drugs show bioavailabilities on the order of 16% with oral dosing and would be excellent candidates for transdermal drug delivery[13]. The third chemotherapy drug, Busulfan, is an alkylating agent also used to treat leukemia. Busulfan, however, has no ultraviolet-visible (UV-Vis) absorption and thus could not be further investigated without significant derivatization[13,14].

Chapter 2. Experimental

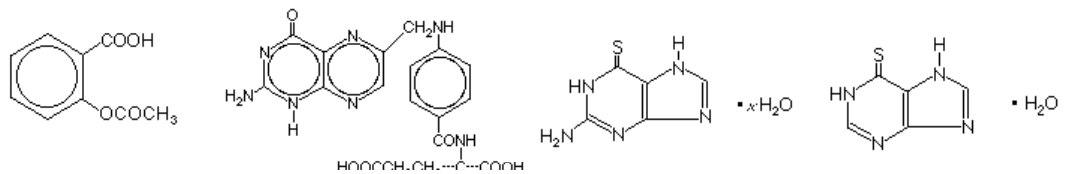
2.1. Materials

Acetylsalicyclic acid (ASA) (Figure 2.1A), was purchased from Fisher Scientific and was used as received for diffusion testing. In addition, folic acid (Figure 2.1B) was purchased from Fisher Scientific and was also used as-received. 6-TG and 6-MP (Figure 2.1C and Figure 2.1D respectively) were purchased from Sigma-Aldrich Inc and were used as received. Sodium lauryl sulfate (SLS) and dimethyl sulfoxide (DMSO) were purchased from Fisher Scientific and used as-received.

HPLC grade water, acetonitrile, *ortho*-phosphoric acid, octanol, heptane, methanol, tetrahydrafuran and acetone were purchased through either Fisher Scientific or the Virginia Tech chemistry supply room. Dithiothreitol was purchased from Sigma-Aldrich Inc. and was used as received. Phosphate buffered saline (pH 7.4≤0.2) was purchased from PolySciences Inc. in a 20x concentrate and was diluted with HPLC grade water.

Poly(ethylene terephthalate) (PET) film (125μm thick) was used as the backing material for the peel testing and diffusion testing. The films were purchased from McMaster-Carr Supply Company. The copper films (25 μm thick) that were used to isolate the adhesive from the probe and stand during thermomechanical analysis (TMA) were purchased from Gould Electronics Inc.

The pressure sensitive adhesive chosen for our study was received from Adhesive Research Inc. and was adhesive formulation MA-24A. The adhesive is a poly(isobutylene) base supplied in a heptane carrier and is a FDA approved adhesive for TDD.



(A) (B) (C) (D)

Figure 2.1 Chemical structure of the active ingredients used in this study.

2.2. Procedures

2.2.1. Chromatography

High Performance Liquid Chromatrography (HPLC) was the test method chosen to determine concentrations of the active ingredients. The HPLC used was manufactured by Hewlett Packard and consists of a series 1050 variable wavelength detector (VWD), autosampler and quaternary solvent delivery system. The HPLC also contained a series 1040 diode array detector (DAD). The VWD allows one wavelength to be examined, while the DAD allows one the ability to scan the entire UV-Vis spectrum as well as focus on specific wavelengths. A Phenomenex Luna 5µ C18 column was chosen to perform the separations. Data analysis was performed using Agilent Chemstation software and Origin® by OriginLab Corporation.

2.2.2. Diffusion System

To evaluate active ingredient permeability, a diffusion system was designed. The first step was the selection of an appropriate diffusion cell. A Franz-type diffusion cell (Figure 2.2) was chosen. This type of cell has been used in a majority of published *in vitro* TDD studies[15,16,17,18]. The cells used in this study were manufactured by Virginia Tech's chemistry glass shop. The diffusion cell consists of two parts: the upper part is the donor compartment (Figure 2.2A) and contains the active ingredient and the carrier adhesive, the bottom part contains the receptor solution (Figure 2.2C), the water jacket (Figure

2.2D) for temperature control, and the sampling port (Figure 2.2B). The receptor solution compartment has a mean receptor solution volume of 6.97≤0.14 mL. A magnetic star-shaped stir bar is placed at the bottom of the receptor solution and ensures consistent mixing in the receptor solution. Phosphate buffered saline was used as the receptor solution unless otherwise stated. Temperature was controlled by pumping water at 37≤1±C through the water jacket with a peristaltic pump.

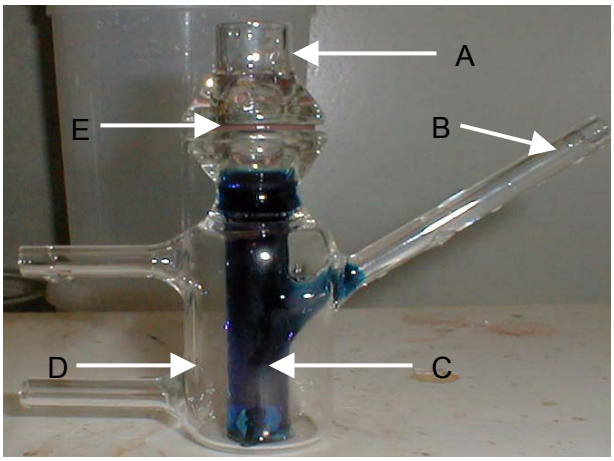


Figure 2.2 Picture of a Franz-type diffusion cell used in this work.

An O-ring seal coupled with a membrane act to separate the top and bottom chambers and allow for 1.13cm^2 of diffusion area. A 50μm poly(dimethyl siloxane) polycarbonate (PDMS-PC) copolymer film was purchased from Specialty Silicone Products, Inc. The copolymerized film provides a material with heterophase and heteropolar structure that more closely simulates the human stratum corneum than other polymeric membranes[5,19]. It is important to note that the polymeric membrane is not used in place of skin, but as a tool to rule out TDD systems that do not work. Once a TDD system is thoroughly tested with the polymeric membrane, the next step in this type of testing is to use skin as the membrane.

2.2.3. Concentration Gradients

HPLC was used to generate analytical methods for determination of transient concentration in the diffusion cell. The calibrations are used to compare HPLC signal intensity to active ingredient concentration in the receptor solution of the diffusion cell. This requires the determination of a suitable mobile phase for the desired active ingredient and the best wavelength (λ) to for characterizing the solution concentration of the active ingredient. The selection of mobile phase is important in that it partially determines the elution time of the molecule being tested. While elution time is less important in single molecule experiments, it is especially important when organic solvents are used to dissolve the active ingredients and their respective signals must be separated. Since the DAD affords the ability to scan from 190 to 420nm UV-Vis spectrum, it aids in the wavelength selection. The wavelength having the highest intensity and the least obtrusive surrounding signals was used in the calibration and subsequent diffusion testing. As a second check, 254nm was used in addition to the active ingredient specific wavelength. Table 2.1 shows the mobile phases and wavelengths used for each active ingredient.

Active ingredient	**λ (nm)**	**Mobile phase (volume:volume)**	**Time (min)**	**A:B**
Acetylsalicyclic acid	225	A: 650 water:350 acetonitrile:2 ortho-phosphoric acid (OPA) B: 1000 acetonitrile:2 OPA[20,21]	0–6.5	100:0
			6.5-10.5	ramp to 70:30
Folic acid	210	A: 1000 water:1 OPA B: 800 acetonitrile:200 water:1 OPA[22]	0-5	98:2
			5-22	ramp to 72:28
6-MP and 6-TG	342	1000 water at pH 2.5 with OPA:1 dithiothreitol[23]	Not applicable	

Table 2.1 Mobile phases and wavelengths used in HPLC experiments.

In order to construct the concentration gradient, solutions of the active ingredient were prepared with concentrations ranging from 0.5μg/mL to 20μg/mL. The intensities of the signals produced by the solutions in the HPLC were then plotted against the

concentrations on a linear scale. Figure 2.3 shows a typical calibration curve, in this case for 6-MP, while Table 2.2 shows the variables used for the linear fit. A linear fit of the data was then performed by the Origin® software program and the resulting equation was used to determine diffused concentrations.

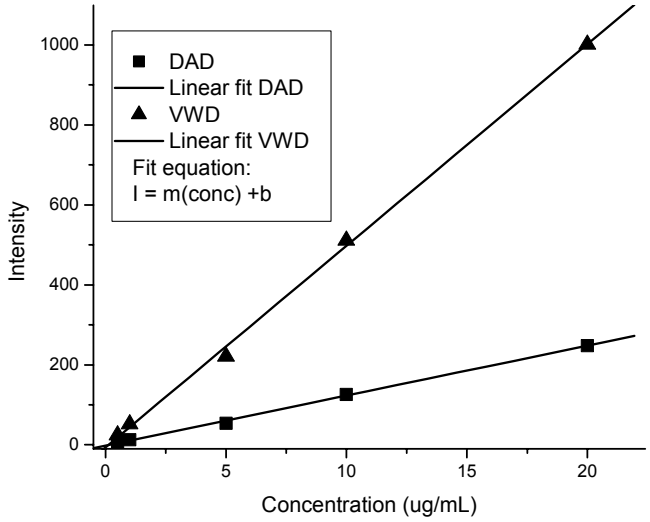


Figure 2.3 The calibration curve for 6-MP.

Detector	m (slope)	B (intercept)	R	Confidence Interval
DAD	12.5≤0.28	-1.98 ≤ 2.87	0.99925	99%
VWD	50.41 ≤ 1.06	-6.39 ≤ 10.91	0.99933	99%

Table 2.2 Calibration curve fitting analysis for 6-MP.

2.2.4. Diffusion

The diffusion tests were performed by mixing a known mass of the active ingredient in a known mass of adhesive. It was necessary to dissolve folic acid, 6-TG and 6-MP in a separate solvent before mixing the active ingredient and the adhesive. ASA was slightly soluble in heptane so no other solvent was needed. The mixture was then spread on the PET films using a doctor blade (500μm thickness) to form a transdermal tape. The transdermal tapes were then placed in a vacuum oven and heated to 80°C for 30 minutes in order to extract the heptane. The tapes were then placed on top of the

membranes and then inserted into the diffusion chamber. Three diffusion tests were run simultaneously for up to 72 hours. 200μL samples of the receptor solution were periodically removed through the sampling port with a 250μL syringe, placed in the HPLC autosampler and tested with the appropriate mobile phase as described previously. Fresh PBS was added to replace the sample removed and calculations were made to account for the removal of the receptor solution and addition of fresh buffer. Since the volume of each diffusion cell differed slightly, the volume of the individual diffusion cell was used to determine mass flux in each experiment.

2.2.5. Effect of Skin Surfactants

Since skin surfactants are sometimes used to aid in transdermal delivery, the effects of SLS and DMSO on the thermomechanical properties and peel strengths of the adhesive were studied. The two surfactants were added to the bulk adhesive at 0.1wt% and were tested by thermomechanical analysis and peel testing, both of which will be described in the following sections.

2.2.5.1. Thermal Analysis

Thermomechanical analysis (TMA) was performed on the pressure sensitive adhesives to determine any changes in the glass transition temperature (T_g). A Perkin Elmer series TMA 7, equipped with the expansion probe was used to perform these experiments. TMA was used because it was found to be more sensitive than Differential Scanning Calorimetry (DSC) for these samples. This was evident as the glass transition temperatures were not detectable by DSC, but were detectable by TMA. The as-received adhesive along with the adhesive and surfactant mixtures were cast onto the copper films (approximately 1.5mm thick) and placed in the vacuum oven at 100°C for 20 minutes. The temperature was set at 100°C to ensure complete extraction of

heptane. Since heptane melts at -90°C, the melting of any residual heptane would mask the T_g of the adhesive. The samples were then removed and allowed to cool to room temperature. Once the adhesive was equilibrated, a second sheet of copper was placed on top of the adhesive, forming a sandwich structure, and frozen to allow for easier handling. Samples measuring approximately 7mm by 7mm were cut from the sandwich and were placed in the TMA. The as-received adhesive samples were cooled and held at -110°C for three minutes before undergoing a temperature scan from -110°C to 50°C at 2°C per minute in a nitrogen atmosphere. The adhesives containing DMSO and SLS were equilibrated at -150°C for three minutes and tested from -150°C to 50°C, to identify characterize the glass transition temperature. Samples of the adhesive/SLS mixture were also cast onto glass to reduce the effect of the copper film's thermal expansion (the copper films had an insignificant amount of expansion). Three samples of each adhesive were measured and the T_gs recorded as the onset of expansion in the sample (just below T_g there is a larger driving force for expansion and therefore a change in the rate of expansion)[24]. The onset for expansion was determined using Origin" by the determination of changes in the slope of the raw data. Since the SLS samples did not show an increase in the rate of expansion, the softening point, the point at which penetration occurs, was also recorded.

2.2.5.2. Peel Testing

The peel testing was accomplished using a TA.XT2i texture analyzer from Texture Technologies Corporation with an aluminum peel test wheel attachment that allows for a 90° peel test. The as-received adhesive and the adhesive mixtures were cast onto the PET films (adhesive thickness was 60μm) and were placed in an oven at 70°C for 20 minutes to remove the heptane and form a tape. From the oven, the tapes were frozen

for easier handling. In order to determine if sweating occurs during processing, the tapes were then annealed in a 100°C for 30 minutes. The annealing, and thus the sweating process, simulates and expedites the diffusion of the skin surfactant through the adhesive. The samples were formed by slicing each tape into a 18mm by 150mm strip then immediately placing it on the testing wheel. The tape was allowed to set for 60 seconds, and then tested at a rate of 5mm/sec. The first 25 mm of the results were discarded while the next 50 mm were recorded for analysis as per the relevant ASTM standard. An example of the typical peel data is shown in Figure 2.4. Three samples of each condition were tested and the average and standard deviation of the peel strengths were recorded in Newtons per centimeter width. The wheel was cleaned with acetone between each peel experiment. The PET was tested at the maximum peel strength measured to ensure that the peel strengths measured were not affected by the backing material.

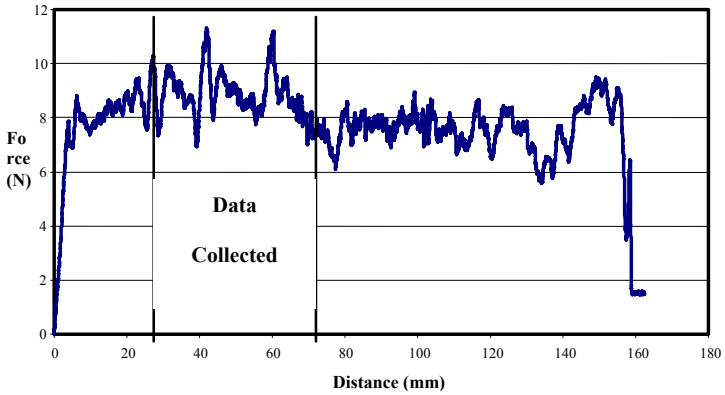


Figure 2.4 Typical peel test data.

Chapter 3. Results and Discussion

3.1. Acetylsalicyclic Acid Diffusion

Since ASA was soluble in the adhesive's carrier, heptane, it was not necessary to dissolve it before mixing with the adhesive. The results of a 24-hour ASA diffusion test are shown in Figure 3.1. Over the 24 hours, 25μg of ASA diffused through the PDMS-PC membrane into the PBS. Only 25μg diffused because there was only 50μg in each adhesive patch tested. As the source mass shrinks, the driving force for diffusion is reduced.

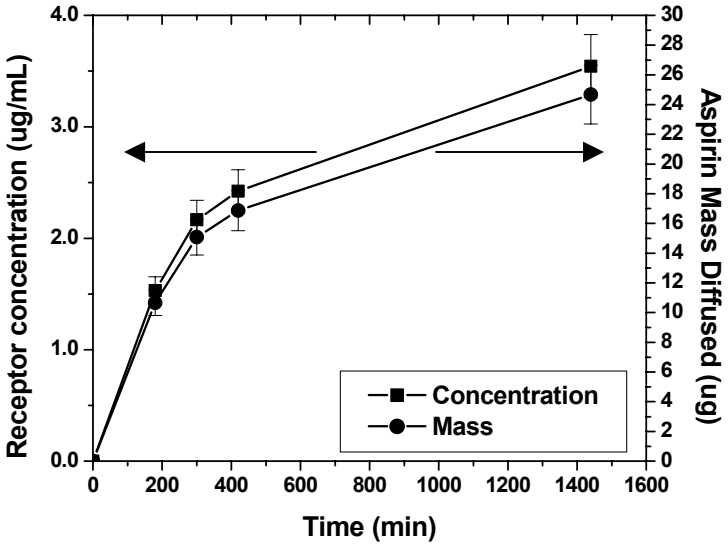


Figure 3.1 Results of the ASA diffusion testing.

McMahon and coworkers published a similar study on the transdermal delivery of ASA in poly(ethylene glycol). Their study employed fresh sha/sha mouse skins as their membranes, PBS as the receptor solution and a 22mL Franz cell. The results of their study along with results from this work are shown in Table 3.1[21]. The table shows a difference of approximately 10 to 20 times more ASA diffused through the polymeric membrane than the mouse skin.

A study by Feldstein and coworkers showed a similar correlation between a 40μm PDMS-PC membrane and human stratum corneum. In their study of 13 different drugs, the polymer membrane was 10 to 20 times more permeable than the human stratum corneum[19]. This shows that while the polymeric membrane can be used to simulate skin for initial tests, TDD systems must eventually be tested on skin to prove efficacy.

Time (hours)	McMahon[21] (μg/cm^2)	Our work (μg/cm^2)
2	0.5	6
4	0.75	11
6	0.75	15

Table 3.1 Comparison of McMahon's and our work.

3.2. Folic Acid Diffusion

Diffusion tests were also run on the folic acid. The first step was to determine an appropriate solvent since folic acid is insoluble in heptane. To find a solvent, 10mg folic acid was dissolved in 10mL of each of the following solvents; PBS, DMSO, methanol (MeOH) and tetrahydrafuran (THF). The samples were then further diluted to concentrations of 2.5 μg/mL then analyzed by HPLC. The results of the testing are shown in Figure 3.2. From this, methanol was chosen as the solvent for folic acid.

The diffusion results for folic acid are shown in Figure 3.3. During these tests only 0.8μg of the 1.4mg available in the patch diffused over 24 hours. The tests were stopped after 24 hours because of an error in the DAD, which shut down the instrument's detectors. One reason for the small amount of diffused folic acid is the low solubility of folic acid in PBS (the solubility of folic acid in water is shown by the dashed line). A second set of experiments utilized octanol as the receptor solution for the diffusion tests. After 72 hours there was no measurable folic acid diffusion. In addition, folic acid's molecular size may also reduce its flux across the membrane, thus reducing the mass of folic acid diffused[7,10,11,25].

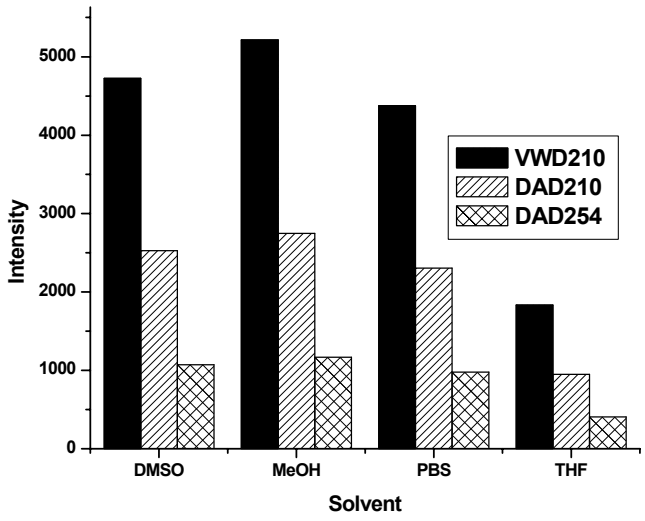


Figure 3.2 Effect of solvent on HPLC anaylsis.

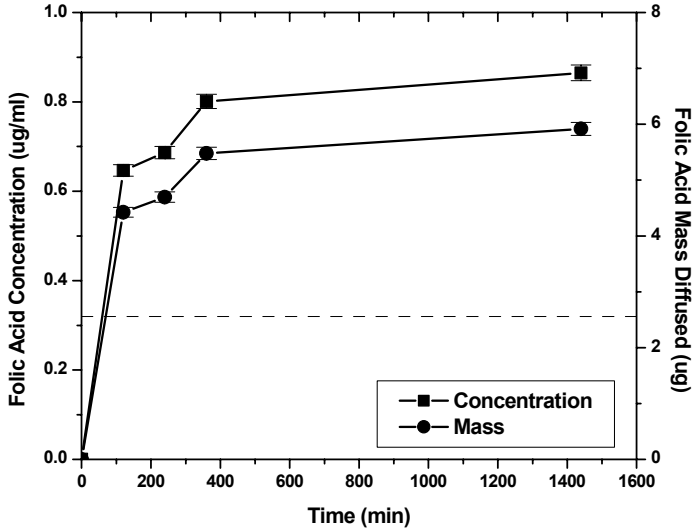


Figure 3.3 Folic acid diffusion results.

3.3. 6-Thioguanine and 6-Mercaptopurine Diffusion

6-MP and 6-TG are insoluble in all common organic solvents and water. In order to prepare the adhesive tapes, 100mg of 6-MP or 6-TG was dissolved in 1M NaOH before mixing with the adhesive. The tapes were placed in the oven at 120°C to drive off the heptane and any water. Due to the fact that these active ingredients are insoluble in

water, PBS, and octanol, there was no measurable diffusion of these compounds after 72 hours.

3.4. Effect of Skin Surfactants

The results of the thermomechanical testing are shown in Figure 3.4 and Table 3.2. Figure 3.4 shows the raw data, in the form of normalized probe position versus temperature. The T_g of the as-received adhesive was measured at -73°C. The addition of DMSO reduced the T_g by 19°C. There was no measurable expansion in the SLS samples so no T_g was reported. The softening temperatures of the adhesives are also shown in Table 3.2. The as-received adhesive had the highest softening temperature (-10°C) followed by the DMSO sample (-54°C) and the SLS sample (-64°C).

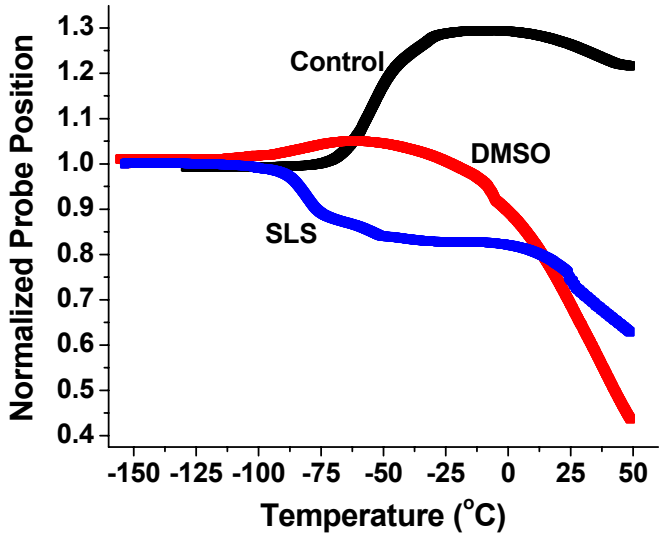


Figure 3.4 Results of the thermomechanical testing.

Sample	T_g (ºC)	Softening Temperature (ºC)	Peel Strength (N/cm)	Annealed Peel Strength (N/cm)
As-received	-79 ± 5	-10 ± 10	18.5 ± 3.2	8.9 ± 2.2
DMSO	-92 ± 5	-54 ± 10	9.9 ± 4.6	11.5 ± 1.9
SLS	Not measurable	-64 ± 5	4.0 ± 1.3	12.6 ± 2.6

Table 3.2 Summary of results from the thermomechanical testing.

The SLS sample posed a number of difficulties in measuring the thermal properties. The first difficulty was caused by sample voids forming by the volatilization of heptane within the sample. The voids caused errors in the thermal testing as the heptane and air trapped inside the voids underwent transitions. The voids may have also caused difficulties in the peel testing. A second problem with the SLS sample was its low solubility with the adhesive; this will also be discussed later. A third problem with the SLS sample is the inclusion of water in the sample. This was evident as a softening point that occurred at about 3°C due to the melting of ice.

The results of the peel testing and the sweating experiments are shown in Table 3.2 and Figure 3.5. It is important to note that all samples failed by means of adhesive failure at our test rate of 5mm/sec. The addition of the surfactants significantly reduces the peel strengths of the adhesives.

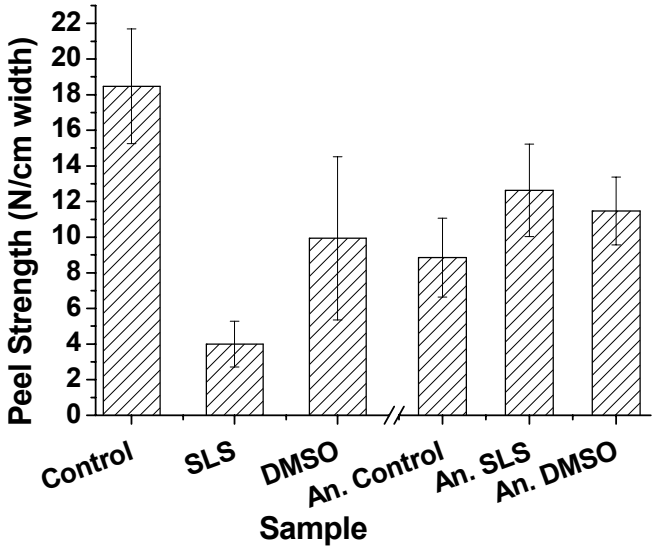


Figure 3.5 Results of the peel testing.

The addition of DMSO and SLS significantly changed both the thermodynamic and adhesive properties of the adhesives. It is also apparent that the surfactants affect adhesion, as there is a considerable reduction in the peel strengths with the addition of

the surfactants. The combination of the two sets of data makes sense. As the T_g/softening temperature of the adhesives decreases, so did the peel strength of the adhesives due to the loss of tack and the lowering of the modulus with the decreasing T_gs. The addition of the plasticizers has little effect on the free volume of the adhesive as it lowers the T_g/softening temperature and the modulus by acting as a compounding agent with a lower T_g.

The low peel strength measured for the SLS sample was also due to other factors. As previously mentioned, the increased number of voids present in the SLS sample lowered both the localized adhesive thickness and the contact area. While the adhesive/void composite had a similar thickness to that of the other samples, the amount of adhesive between the backing material and the wheel was reduced. The reduced contact area also lowers the amount of mechanical interlocking. The combination of these properties would lower the peel strength on any PSA as it did for the SLS mixture.

The effect of annealing was useful in determining changes in the adhesives. There was a reduction in the peel strength of the as-received adhesive, which is thought to be due to the reduction in the amount of residual heptane and a reduction in tack. In addition, there was no sign of sweating of the surfactants. If sweating was to occur, the SLS and DMSO would migrate to the surface and possibly reduce adhesion, however, the opposite seems to have occurred. The surfactants seemed to be better distributed throughout the adhesive as the peel strength of both the SLS and DSMO samples increased.

The increase in the SLS sample's peel strength could also be due to the higher driving force towards solubilizing the SLS into the adhesive. Another factor leading to this conclusion is the reduction in the number of voids present in the peel sample.

Chapter 4. Accomplishments and Conclusions

Concentration profiles were developed for ASA, folic acid, 6-MP and 6-TG from diffusion test results. This data allows future workers the ability to link concentrations diffused during diffusion testing to intensities on our HPLC. Initial diffusion tests were also completed for the four active ingredients studied. From these tests it can be concluded that octanol, water and PBS receptor solutions are not appropriate for testing the diffusion of folic acid, 6-MP and 6-TG due to the limited solubilities of the active ingredients in each solvent. Further diffusion testing must be done with other receptor solutions for these active ingredients to become viable candidates for a TDD system.

As for the addition of skin surfactants to the PIB adhesives, it was shown that the addition of skin surfactants reduced the T_g and softening temperature of adhesives. Furthermore, the addition of skin surfactants also reduced the peel strength of adhesives indicating the existence of a trade-off between better transport and better adhesion of the PSA. This trade-off may become a limiting factor in the development of additional TDD systems, and if more systems are to be developed successfully, further study of specific polymer-drug systems is essential.

Chapter 5. Future Work

There are a number of possible areas for future work. First, the diffusion experiments could be continued. Another group is currently doing the ASA work, so there may be fewer unique opportunities working with ASA. However, the folic acid work is interesting, as it could address a important need in pre-natal care, and is currently being studied by Dr. Thatcher in the College of Veterinary Medicine and Dr. Long's group in the Chemistry department. The problem posed by the solubilities of the 6-MP and 6-TG could probably be overcome by using NaOH as the receptor solution instead of organics or PBS. This, however, further changes the process in that it maybe less physiologically relevant.

Since is was shown that the polymeric membrane allowed 10 to 20 times more ASA to diffuse than the fresh mouse skin, a better skin substitute should be used for further testing. Recently, Organogenesis Inc has developed an artificial skin substitute, TESTSKIN II. However, its use was cost prohibitive at \$1000 per 45cm^2 sample. Nor is there any literature proving its efficacy in TDD testing.

Another interesting area for work is determining concentrations and the pharmacokinetics of Busulfan. While it has been given to cancer and marrow replacement patients for over 40 years little is known about concentrations in the blood stream as busulfan is difficult to trace[14,26].

Chapter 6. References

[1] H. Tan, W. Pfister; *Pharmaceutical Science and Technology Today*; **2**, 2 (1999) 60-69

[2] Venkatraman, R. Gale; Biomaterials; **19** (1998) 1119-1136

[3] J. Bouwstra; Colloids and Surfaces A: Physicochemical and Engineering Aspects; **123-124**; (1997) 403-413

[4] D. Satas, ed.; Handbook of Pressure Sensitive Adhesive Technology: "Hospital and First Aid products"; New York: Van Nostrand Reinhold (1989)

[5] J. Houk & R. Guy; *Chemical Reviews*; **88** (3) (1988) 455-471

[6] K. Wilhelm, C. Surber, H. Maibach; *The Jour. Of Investigative Dermatology*; **96**, 6 (1991) 963-967

[7] V. Shah, D. Werkema, N. Vallespi I Salvado; *Adhesive Technology*; September (1998)

[8] J. Mark, ed.; Polymer Data Handbook: "Poly(isobutylene), butyl rubber, halobutyl rubber"; New York: Oxford University Press (1999)

[9] D. Satas, ed.; Handbook of Pressure Sensitive Adhesive Technology: "Butyl Rubber and Polyisobutylene"; New York: Van Nostrand Reinhold (1989)

[10] J. Hirvonen, L. Murtomaki, K. Kontturi; *Jour. Of Controlled Release*; **56** (1998) 33-39

[11] J. Hirvonen, L. Murtomaki, K. Kontturi; *Jour. Of Controlled Release*; **56** (1998) 169-174

[12] M. Cronin, J. Dearden, G. Moss, G. Murray-Dickson; *European Jour. Of Pharmaceutical Sciences*; **7** (1999) 325-330

[13] W. Foye; Priciples of Medicinal Chemistry; Philadelphia, Lea & Febiger (1989)

[14] M. Quernin, B. Poonkuzhali, C. Montes, R. Krishnamoorthy, D. Dennison, A. Srivastava, E. Vilmer, M. Chandy, E. Jacqz-Aigrain; *Jour. Of Chromatography B*, **709** (1998) 47-56

[15] D. Friend; *Jour. Of Controlled Release*; **18** (1992) 235-248

[16] D. Skerrow & C. Skerrow ed.;Methods in Skin Research: "Skin Permeability"; New York: John Wiley & Sons (1985) 407-431

[17] M. Bonferoni, S. Rossi, F. Ferrari, C. Caramella; *Pharmaceutical Development and Technology*; **4**, 1, (1999) 45-53

[18] C. Gummer, R. Hinz, H. Maibach; *International Jour. Of Pharmaceutics*; **40** (1987) 101-104

[19] M. Feldstein, I. Raigorodskii, A. Iordanskii, J. Hadgraft; *Jour. Of Controlled Release*; **52** (1998) 25-40

[20] F Kees, D Jehnich, H Grobecker; *Jour. Of Chromatography B*; **677** (1996) 172-177

[21] G McMahon, S O' Conner, D Fitzgerald, S le Roy, M Kelly; *Jour. Of Chromatography B*, **707** (1998) 322-327

[22] Phenomenox Inc. Torrence Ca, USA

[23] J Bonnefous, P Gendre, M Guillaumont, A Frederich, G Aulanger; *Jour. Of Liquid Chromatography*, **15**, 5 (1992) 851-861

[24] W.J. Sichina; Thermal Analysis Application Note "Characterization of Polymers by TMA"; Perkin Elmer Instruments; Norwalk, CT (2000)

[25] Y. Kalia, V. Merino, R. Guy; *Dermatologic Clinics*; **16**, 2 (1998) 289-299

[26] J. Blanz, C. Rosenfeld, B. Proksch, G. Ehninger, K. Zeller; *Jour. Of Chromatography Biomedical Applications*; **532** (1990) 429-437