J Pharm Biopharm Res, 2022, 4(1): 256-270
DOI: 10.25082/JPBR.2022.01.003

RESEARCH ARTICLE

Transdermal drug delivery systems: Analysis of adhesion failure

Zachary Brooks[1] **Tushar Goswami**[1] **Amy Neidhard-Doll**[2] **Tarun Goswami**[1*]

[1] Department of Biomedical, Industrial and Human Factors Engineering, Wright State University, Dayton, OH 45435, USA
[2] Department of Electrical and Computer Engineering, University of Dayton, Dayton, OH 45469, USA

Correspondence to: Tarun Goswami, Department of Biomedical, Industrial and Human Factors Engineering, Wright State University, Dayton, OH 45435, USA; Email: tarun.goswami@wright.edu

Received: May 1, 2022;
Accepted: June 9, 2022;
Published: June 13, 2022.

Citation: Brooks Z, Goswami T, Neidhard-Doll A, *et al*. Transdermal drug delivery systems: Analysis of adhesion failure. *J Pharm Biopharm Res*, 2022, **4**(1): 256-270. https://doi.org/10.25082/JPBR.2022.01.002

Abstract: The most critical component of the TDDS is the adhesive, which is responsible for the safety, efficacy and quality of the patch. For drug delivery to successfully occur, the patch must adhere to the surface of the contact area. If a patch has inadequate adhesion, it is likely to fall off before the entire delivery period has been satisfied, leading to risks for the patient and others who may encounter the patch. Despite the critical concerns associated with the adhesive properties of the patches, the adhesion quality and failure mechanisms have not been fully studied. If certain molecules encounter the adhesive, it may cause irreversible altering of its chemical composition, which could render it unsuitable for transdermal applications. In many cases of TDDS failure, sweat is believed to be a culprit responsible for causing adhesive failure. The goal of this project is to investigate the chemical composition of the adhesive layer of a transdermal patch. The patch sample is a Sandoz Estradiol Transdermal System manufactured by Noven Pharmaceuticals, Inc., designed to deliver 0.1mg per day and contains 1.56mg of Estradiol USP, the active ingredient. By analyzing the chemical composition of a patch that has not been worn, versus a patch that has been worn, it may be possible to determine the chemical interaction that causes adhesive failure. Fourier Transform Infra-Red (FTIR) Spectroscopy (OPUS FTIR Spectrometer) was performed on an unused estradiol TDDS patch immediately after opening, and again after 24 hours in ambient air to investigate the potential for oxidation. The IR Spectrum was then analyzed, and the peaks were reviewed. The IR Spectra for the sample left out for 24 hours indicated lengthened peaks corresponding to C=O, C-O, and O-H, a decreased transmittance, and a wider bandwidth in those regions. Based on these results, it can be determined that oxidation does occur on a patch sample that is exposed to ambient air. In future works, additional patch samples will be collected and used for an extensive IR and UV analysis. By comparing the IR and UV Spectrum graphs of "used" patches that did not fail, with "failed" patches, it may be possible to identify a cause for premature patch failure related to sweat interactions.

Keywords: TDDS, Estradiol, IR spectroscopy, FTIR, adhesion, Transdermal, drug delivery

1 Introduction

It is common for the skin to be used as a drug delivery medium. Transdermal drug delivery systems (TDDS), which are more commonly known as "patches" are specifically designed to deliver a therapeutically effective amount of drug across a patient's skin [1]. Drug delivery is focused on the skin for the treatment of systemic pathologies or localized diseases. The TDDS act to limit the blood levels of the active ingredient [2]. Although the term "patches" is considered synonymous with TDDS, some systems are actually considered "plasters" which act to localize the effect of drugs. The patch style of drug delivery has been gaining popularity in recent years. This can be partly attributed to the ability of TDDS to deliver drugs over a lengthened time frame. Additionally, TDDS are easy to administer, as the location and release rate of the drug is predetermined.

The most critical component of the TDDS is the adhesive, which is responsible for the safety, efficacy and quality of the patch. For drug delivery to successfully occur, the patch must adhere to the surface of the contact area. If the patch is lifted off one section of the contact area, or if the patch falls off, the delivery capabilities of the patch are severely compromised. If a patch has inadequate adhesion, it is likely to fall off before the entire delivery period has been reached. If this occurs, then the patch will need to be replaced more often, which results in higher costs. Additionally, if the patch falls off prematurely, it may end up accidentally attached to another person. This type of occurrences has been reported when individuals hug or have a skin surface contact another person's patch. The danger in this is that if an individual

is unknowingly and unintentionally exposed to certain drugs, it could cause serious medical problems and potentially death. This danger is heightened if the patch is dropped on the ground and discovered by children, who may not understand what it is intended for and are likely to be exposed to the drug. Despite the critical concerns associated with the adhesive properties of the patches, the adhesion quality and failure mechanisms have not been fully studied.

Patch adhesion is often secured by using materials known as pressure-sensitive adhesives (PSAs). These materials are capable of bonding to surfaces with light pressure application, and do not leave any visible residue when removed [23]. In the patches, a PSA serves as the carrier for the active ingredient, while controlling the release rate of the drug and maintaining adhesion to the contact surface.

There are three major classifications of patches: matrix systems, or drug-in-adhesive systems; reservoir systems; or membrane-controlled systems [1, 2]. Figure 1 detailing the three major classifications can be found below. There are several requirements for PSAs for their use in transdermal patches. The PSA material must be biocompatible, compatible both physically and chemically with drugs are other components of the patch, and capable of securing adhesion in amounts that are within the required thickness of the adhesion layer of the patch.

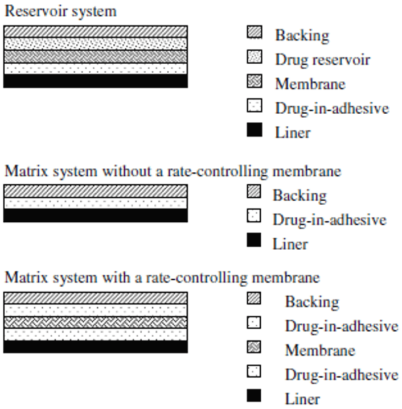

Figure 1 Major Classifications of TDDS [1]

There are several types of PSAs used in TDDS patches. The first type are PIB-based adhesives, which are considered the earliest used [3]. The patches are created by mixing different molecular weight PIBs to create the desired characteristics. These types of adhesives are very weak to oxidation and have a low air and water vapor permeability [4]. The second type are acrylic-based adhesives, which combine hard and soft monomers at different ratios to engineer the characteristics of the resulting polymer. An example of the types of monomers used can be found in Table 1. This type of PSA is more resistant to oxidation, are colorless, transparent, and do not turn yellow when exposed to sunlight [5]. Silicon-based adhesives are also used and contain poly-dimethyl siloxane and silicate resin. The properties of the adhesive depend on the ratio of the two materials. Silicon-based adhesives are an excellent choice for drug delivery, but also tend to result in drug crystallization [2, 6–8] There are other types of PSAs that are used that contain novel combinations of materials and do not fall into the three major categories.

Table 1 Monomers commonly used in acrylic-based adhesives [2]

Soft monomers	Tg (°C)	Hard monomers	Tg (°C)
Butyl acrylate	-54	Methyl methacrylate	105
isobutyl acrylate	-40	Vinyl acetate	29
2-Ethyl hexyl acrylate	-85	Styrene	100
Ethyl acrylate	-22	Acrylonitrile	100

As can be seen in Figure 1, there are several main components in a TDDS system. The main components are the release liner, backing, membrane, and PSA. The release liner acts as a barrier between the patch and environment in storage, preventing premature drug release. The backing is simply a flexible material used to promote the appearance of the outer portion of the patch. The membrane is an optional addition which has diffusion properties which are used to control the delivery of drug to the skin. The PSA was explored previously.

The adhesive properties of the patch are described using specific terminology. For example, the tack represents an adhesives ability to initially bond to the contact surface under light

pressure of a small duration. Since patches are often applied to the body in low pressure scenarios, low-tack PSAs are necessary. Shear adhesion, also known as holding power, evaluates the matrix's resistance to flow. Shear adhesions ensures that the patch will stay on the skin for a certain period of time, regardless of any stresses caused by clothing items or body motions. Peel adhesion is the force necessary to remove the patch from the contact surface. Peel adhesion ensures that the removal process is painless and does not leave behind residue or damage to the surface of the skin.

Adhesion of the TDDS to the contact area is crucial to maintaining optimal and expected drug delivery. Absorption of the drug into the skin is determined by many factors, such as skin sites, skin thickness, skin temperature, blood flow, lipid concentration, number of hair follicles, skin cleansing, sweat gland function, ethnic group, and the pH of skin surface [1]. Different combinations of these factors can result in different adhesive results and thus absorption of the drug. Thinner skin or compromised skin could result in increased drug concentrations, whereas thicker skin may result in lesser drug concentrations.

The fundamental requirement for adhesion to occur is governed by thermodynamics. The measured surface energy of the adhesive must be equal to or less than that of the contact surface [24]. The surface energy on clean, dry human skin is roughly 27 dyn/cm [1, 9] or 28-29dyne/cm [2]. Similarly, to drug absorption, there are many factors that can influence the surface energy of skin, which affects the adhesion of the patch. An increase in surface energy is expected on dirty or unwashed skin. As humidity and temperature increases, the surface energy of skin increases as well. When the TDDS is applied to skin, an increase in adhesion is seen as its temperature increases to that of the skin. As the adhesive drifts on the surface of skin, the adhesive bond between the skin and PSA increase until reaching an equilibrium point as the temperature equalizes between the skin and the patch [1]. As the skin is hydrated and the stratum corneum (the outer layer of skin) swells, the cohesive strength of the stratum corneum is reduced. Reduced adhesive contact, diminished drug concentration, and the weakening of the outer layer of skin all cause the adhesive strength of the patch to be decreased [24].

If the conditions required for the patch to adhere to human skin are not met, failure of the patch occurs. The most common failure of a TDDS is failure of adhesion or cohesion. There are four major cases of failure associated with adhesion and cohesion, which can be found in Figure 2 and 3. Case 1 occurs when the patch is peeled cleanly from the skin. This is the expected mode of failure. Case 2 occurs when the patch is peeled but leaves behind the adhesive on the skin surface. Case 3 occurs when adhesive is left on the skin and on the patch and is an example of cohesive failure. Case 4 is simply a combination of adhesive and cohesive failure [23]. The type of failure that occurs is used to evaluate the TDDS as well as identify potential failure mechanisms.

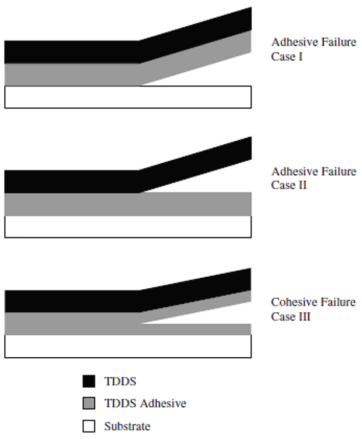

Figure 2 Adhesive and Cohesive Failure in TDDS [1]

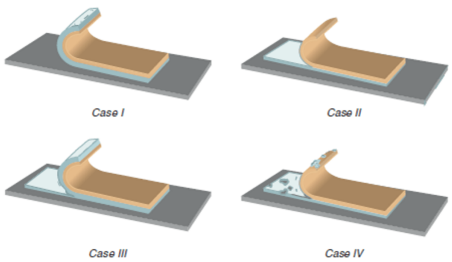

Figure 3 Modes of Failure in TDDS [2]

1.1 TDDS Adhesive Analysis

There are several methods used to predict the performance of patch adhesives in-vivo. For example, the adhesion performance of a patch is evaluated using an FDA score chart in which the patient selects a score based on the amount of the patch which adhered to the skin during the usage period. There are also tests that evaluate the peel adhesion of the patch by applying different rates of peeling to a patch that is placed on the skin. These studies have determined that the slower the patch is removed, the more adhesive is also removed. The tack strength can be evaluated similarly by using quick-stick tests and generating stress-strain curves after the patch is removed. In-vitro tests are also attempted in which the patch is applied to different plates with a similar surface energy to that of skin, such as stainless steel (40 dyne/cm) or poly(tetrafluoroethylene) (PTFE) [2, 10–12].

There are also several organizations that release specifications on transdermal delivery system performance. The American Society for Testing and Materials (ASTM) has specific requirements for testing relating to the adhesive properties of the transdermal patches. The Pressure Sensitive Tape Council also has similar specs that are relevant due to the use of the pressure sensitive adhesive. The peel adhesion is assessed using ASTM D330 and PSTC 101, which evaluates the force required to remove adhesive from a rigid substrate. Static shear, the ability of tape/adhesive to resist the application of static forces parallel to the backing, is tested using ASTM D3654 and PSTC 107. ASTM D979 evaluates the probe tack of a patch, by testing the force necessary to remove adhesive from an inverted probe [1, 42]. PSTC 4 evaluates release force, by testing the force required to remove an adhesive strip from the release liner. PSTC 6 evaluates rolling ball tack, by testing the ability of adhesive to bond with the surface of another material under brief contact with extremely low pressure [1, 42]. PSTC 16 evaluates the loop tack, by testing the force necessary to remove a loop of adhesive from a substrate.

1.2 TDDS manufacturers

There are many companies that are currently producing transdermal drug delivery systems. The patches have a variety of different designs, and companies are currently poising themselves to provide unique contributions to the field, giving them the professional edge. One such company is 3M Drug Delivery Systems. 3M has previously pioneered the design of medical tape, which they have added to the design of their patches in order to ensure adequate adhesion time. Additionally, 3M provided their tape expertise in a partnership with Dow Corning, bringing their material and drug knowledge to provide new framework for future patches. This system combines the 3M™ Scotchpak™ Release Liners and Dow Corning® brand BIO-PSA Silicone Adhesives [33].

Another leading manufacturer, Zosano Pharma Corporation is pioneering the use of microneedles in transdermal delivery systems. Their microneedles negate the need for stronger adhesives by requiring a much shorter wear time. They also serve a secondary function, by assisting in the delivery of drugs into the circulatory system.

Tapemark is also taking a unique approach to the transdermal drug delivery market. Tapemark developed the IontoPatch, which uses the principles of IontoPhoresis to start and stop the delivery of drugs through the skin [35]. These units have a self-contained flex battery, producing an electric current that directly influences the movement of drug molecules. The IontoPatch has several versions, each featuring a different dosage level and treatment time.

Transdermal drug delivery systems have also transitioned to a recreational market as well. The company Transdermal Solutions LLC and several others have recently begun to market a hangover defense patch. Transdermal Solutions' model, the Party Patch, claims to be a natural hangover defense. The patch utilizes traditional transdermal drug delivery techniques to deliver high doses of vitamins over a time frame of less than one day, alleviating the symptoms commonly experienced during hangovers.

With the growing popularity of transdermal patches, there are several big-name market leaders currently producing the patches. Among the top market leaders are 3M, ProSolus, Inc., Zosano Pharma Corporation, MedPharm, Tesa Labtec GmbH, Medherant Limited, Tapemark, Toyochem Co. Ltd, and several others [34, 37–39]. The patches are marketed to a wide range of individuals. The patches are used to treat things such as motion sickness, smoking addicton, and ADHD. TDDS also have a strong hold in birth control, blood pressure control, osteoporosis prevention, and alleviation of menopause symptoms. Additionally, the patches have spread into the recreational market with products such as hangover defense patches and focus patches.

Since the popularity of TDDS usage has surged in recent years, there is a plethora of data available to the FDA. Many patients have reported complaints of failure when using the patches. Some of the most common reports involve failure due to environmental condition, requirement

to use tape to hold the patch on, increase in cost associated with patch failure, and lack of quality. A summarized table of reports can be found in Table 2.

Table 2 FDA record of complaints for TDDS due to failure [1]

No.	FDA record
1	Heat, cold, sweating (respiring) and showering prevent the patch from sticking to surface of skin for more than one day.
2	A new has to be applied daily,
3	The patches fall off during bathing and sleeping, has resorted to using medical tape to help patches. he is not getting his money's worth
4	from this product.
5	Patches fall off completely during bathing or swimming patches sometimes fall off during walking, sweating will cause patches to not stick.
6	(Compared to a brand previously used), the patch is thicker and would not allow transmission and evaporation of body sweat. As a result it lifts off spontaneously within 2 days or after a couple of warm showers.
7	Unable to make the patches adhere after the first day. The reporter was given various types of tape and bandages too but none have proven satisfactory The patients reported that the remedy does indeed work well when sticking, but not too long.
8	Patient complained that the patch would not stick to the skin. The patient was using scotch tape to try to keep the patch on.
9	Adhesive not sticking, patient was told to use adhesive over patch by R.N.
10	Patches will simply not stay on, Reporter called the pharmacy and they suggested to covering patch with an adhesive strip.
11	A patient reported that the patches were not sticking to her skin. The reporter contacted the manufacturer.
12	Eventually, she reached a representative who advised several tips to the patient that may solve the problem,
13	Avoid certain soaps. Use paper tape. Try taking it out of the pouch and waving it in the air for 15 s before applying. The tricks did not work. Patches should with no tricks.
14	Patch does not stay on. feels that for the money he is spending on this product he should not have to resort to more money to ensure that the product stays on.
15	The patches will not stick and repeatedly fall off. It is causing patients to the number of refills they are obtaining in a month.
16	Customer informed to use adhesive to keep the patch on. The patches are quite and this problem of them not sticking can become quite costly.
17	Does not consider the effectiveness of these patches to as advertized for the reason that the therapeutic effect is degraded due to unreliable properties.
18	Patient had on product for about I year with no complications. Upon refilling prescription, patient complained of loss of efficacy. Also, rash and itching at administration site. Applying new patch from a different lot efficacy returned.
19	Patches are not sticking, and patient is experiencing redness, swelling and itching at patch site,
20	Patch pulled skin away causing bleeding/inflammation. (A different) brand patch caused no skin reaction.
21	(Compared to a previous brand), the esthetics and the performance of the patch is not the same. These patches are and thicker. The skin patch was abraded and wet to touch, when removing the patch, skin (adhered to it and left an open sore). Removal Of patch is very difficult. Tearing skin upon removal.
22	Tie adhesive is so sticky that it can tear or irritate elderly patients' fragile skin. This has occurred on more than one occasion.
23	The sticks excessively to the clear plastic backing (release liner) and resulted in tearing of the patch and removal of significant adhesion.
24	RN. reported that patch could not be removed from protective to apply to patient's skin.
25	Patch would not flex with the patient's skin and therefore come off. The patches would not Stay on the skin they re-applied.
26	The customer feels the patches are too stiff and do not conform to body.
27	Patches wrinkle and fall off easily,
28	It (the patch) does not stay on the skin very well. The patch is specifically not adhering around the outside. It gaps up' or tents up'.
29	Within 24 h the patch begins to curl and fall off.
30	The look/feel/stroll of the two different lot numbers were definitely not same
31	There are small crystals on three patches.
32	Residents (patients) complained about feeling of adhesive going on and coming off.
33	Patient stating, he had used these patches for more than I year and is familiar with them. He claims that these patches had more adhesive on them than usual patches difficulty in removing, more redness on skin area than usual.
34	Female with poor vision admitted to the emergency room with the patch lodged in her throat. The patch apparently became stuck to the patient's sweater fell into her food.
35	Transdermal systems are coming off the patients, finding in their clothes, hair, *etc.*

1.3 Pharmacokinetics

There are several advantages and disadvantages to using transdermal drug delivery patches. One of the biggest advantages is patient compliance and ease of use. Oral drug delivery methods are one of the most popular delivery techniques for the same reasons. Despite those similarities, TDDS and oral delivery methods have different pharmacokinetics. Transdermal drug delivery has three main parts. First is the lag time which is the time until plasma concentrations are achieved in the body. Next, is a period of constant drug delivery with a steady plasma concentration. Finally, is a declining phase occurring after the patch has been removed [46]. Oral drug delivery is different, as it begins with the time before the drug reaches the gut, followed by systemic circulation where the drug is absorbed, and finally the drug is eliminated from the body [47]. This difference is one of the defining features of the transdermal system. By reaching a peak drug concentration in the plasma, the TDDS manages to steadily release the drug into the body over an extended time period. This allows the drug release to be easier to predict compared to the oral delivery.

Most of the transdermal patches utilize passive transdermal delivery. For a drug to be compatible with this type of delivery, there are a few general requirements. The drug must have a molecular weight below 500, a melting point below 200°C, and a logarithmically transformed

octanol-water partition coefficient [41]. In order to predict the pharmacokinetics, there are two predictive approaches. The first is the empirical approach, relying on data gathered from experiments that utilize animal or human skin. The second is the theoretical approach, which analyzes the possible entry routes and the chemical properties of drugs.

There are many empirical models that are commonly used. They all use experimentally determined permeability coefficients that correlate with physicochemical properties in zero or first order equations [41]. One of the most popular is the Potts and Guy model, represented in equation 1: Potts and Guy Model for TDDS Drug Delivery [41].

$$\log \mathrm{Kp} = -2.72 + 0.71 \log K_{\mathrm{oct}} - 0.0061\mathrm{MW} \tag{1}$$

In the Potts and Guy model, there are several coefficients. The first, "Kp" represents the permeability coefficient. Next, "Koct" represents the octanol-water partition coefficient. Finally, "MW" is the molecular weight of the drug.

The theoretical models focus on using molecular properties and physicochemical characteristics that can be determined without experimental testing. Together, they are used with a zero or first order equation to predict the transdermal pharmacokinetics resulting from that drug suspending in a TDDS. Despite their existence, research has shown that there is a minimal correlation between the characteristics and the resulting transdermal drug delivery [41]. This is estimated to be due to the tendency for interindividual variability during in-vivo scenarios. Transdermal drug delivery variance is also affected by skin thickness, metabolism, gender, age, and other factors.

In order to provide a better prediction for transdermal pharmacokinetics, a multiple regression equation proposed. They determined that the best predictor for drug delivery, focusing on the maximum concentration in the plasma, is the number of hydrogen bond acceptor groups in the drug [41]. Using their multiple regression analysis, they developed equation 2: Formula predicting the maximal plasma concentration from transdermal drug delivery [41].

$$\begin{aligned} C_{\mathrm{max}} =& 6.055\mathrm{e}-07 \log K_{\mathrm{oct}} + 8.691\mathrm{e}-07\mathrm{HA} + 1.075\mathrm{e}-06\ \mathrm{V} \\ & - 1.91\mathrm{e}-06E - 2.84\mathrm{e}-06 \end{aligned} \tag{2}$$

In the equation, "Cmax" refers to the maximum plasma concentration. The term "Koct" is the octanol-water partition coefficient. Next, "HA" refers the the number of hydrogen bond acceptor groups. The term "V" is the McGown characteristic volume, in units of $\mathrm{cm}^3\mathrm{mol}^{-1}/100$. Finally, "E" refers to the solute excess molar refractivity, in units of cm3mol-1/10. This formula can give better insight into the effectiveness of new drugs that are considered for use in transdermal delivery applications.

2 Materials and experimental methods

The goal of this project is to investigate the chemical composition of the adhesive layer of a transdermal patch. One of the most common patch failures is due to sweat causing the adhesive to fail. When a substance is added to the PSA, unpredictable alteration of the adhesive properties can occur due to its plasticizer/anti-plasticizer effect [2]. By analyzing the chemical composition of a patch that has not been worn, versus a patch that has been worn, it may be possible to determine the chemical interaction that causes adhesive failure. If the chemical or protein is discovered, the adhesive layer could be engineered to prevent interaction with the adhesive, preventing this type of failure from occurring.

The patch is designed to deliver 0.1mg per day and contains 1.56mg of estradiol USP, the active ingredient. The patch also contains several inactive ingredients, consisting of acrylic and silicon adhesive, oletyl alcohol, dipropylene glycol, povidone, coextruded backing film, and polymer release liner. The multi-polymeric adhesive is made of the acrylic and silicon adhesive combined. The dipropylene glycol is a plasticizer and solvent. Povidone is the polymeric vehicle for dispersing and suspending the drugs [27]. The chemical structure of the adhesive is found in Figure 4.

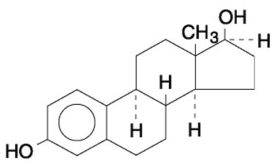

Figure 4 Chemical Structure of Estradiol Adhesive [27]

The Estradiol patches are designed to prevent postmenopausal osteoporosis and treat a variety of symptoms due to menopause. The patches are applied in a two-day system. The patch should remain on the skin for 3-4 days, then be replaced with a new patch. The manufacturers provide the following chart in Figure 5 to patients to plot the days they need to switch out the patch. The estradiol patches require a prescription to obtain, and an 8-pack without insurance will cost roughly $90, resulting in about $11 per patch.

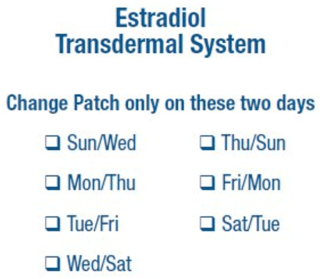

Figure 5 Patient Chart representing optimal days to change the patch [27]

The Experimental Plan involves used and unused patches. Used patch samples were requested from private volunteers within the lab group. The patches will be documented when they arrive at the lab. For the used patches, researchers will record the time that the patch had been worn, the level of activity of the user, if a failure occurred, and if the user had showered with the patch on. The unused patches can follow a similar documentation as they are opened and used for testing purposes.

Fourier Transform Infra-Red (FTIR) spectroscopy used on both unused patch and used patch samples. The unused patch sample analyzed after 24 hours and/or 3-4 days in ambient air, as this will give indication of any atmospheric interaction with the adhesive matrix that may result in changes in chemical composition.

A Scanning Electron Microscope (SEM) used to analyze both unused patch and used patch samples. During this analysis the surface of the adhesive will be evaluated and compared between the samples. This method will determine if there are irregularities in the adhesive layer resulting from patch use. The unused patch sample will also be imaged after 7 days in ambient air, as this will give indication of any atmospheric interaction with the adhesive matrix.

An optical microscope used to characterize the surface of both an unused patch and used patch samples. The surface of the adhesive will be analyzed to determine if there are apparent differences between patch samples.

The evaluation of the unused patches may occur at specified time points after opening, such as 1, 3, 7, and 12 hours after opening. Fourier Transform Infra-Red (FTIR) Spectroscopy (OPUS FTIR Spectrometer) was performed on an unused estradiol TDDS patch. The patch remained in the original wrapping until just before testing occurred. To prepare the sample, the top of the patch container was cut open and the patch was removed. The estradiol patch is an optically clear patch. The release liner is severed in the middle, and each piece was attached to the left and right side, like the backing of a band-aid. The right side of the release liner was carefully peeled from the patch sample. To prepare the FTIR, a background sample was used to establish a baseline. Next, the patch sample was loaded onto the sample platform, ensuring that the side with the release liner removed is over the sampling area. The top detector was then lowered into position opposite the lower detector.

3 Results

The IR spectroscopy was performed, and an IR graph, Figure 6, was generated.

The patch sample was left overnight (24 hours) in ambient air conditions. This allowed for atmospheric interactions and potential oxidation of the sample. The same procedure used previously for the patch sample was repeated, this time generating an IR spectrum for the patch sample 24 hours after opening, found in Figure 7.

The IR Spectrum graphs were then analyzed, and the peaks were reviewed in accordance with an IR Spectrum table [49]. The results of the analysis are found below in Table 3 and 4. There are many components that are contained in the sample, and it is important to review the chemical structure of the components in comparison to the chemical bond results from the IR Spectrum analysis. Additionally, the IR Spectrum for each individual component can be compared to that of the sample.

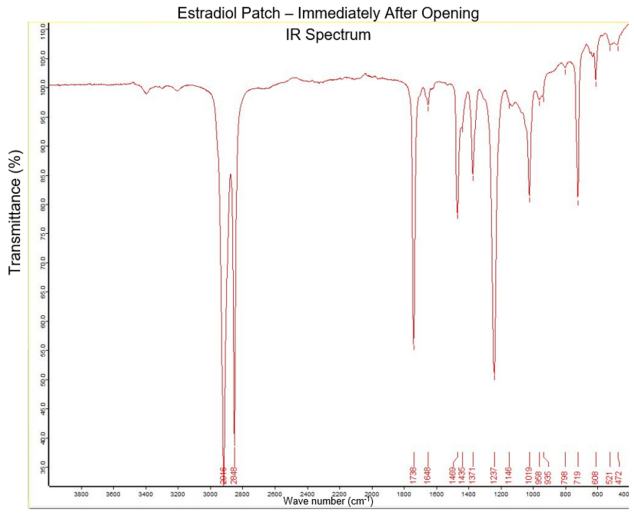

Figure 6 IR spectrum for Estradiol Patch immediately after opening

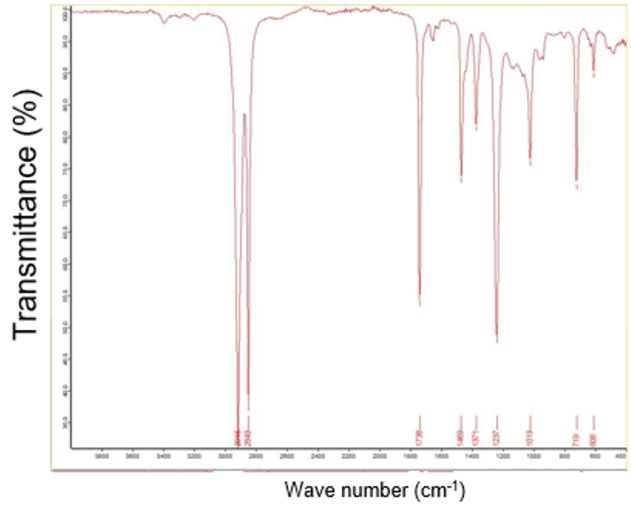

Figure 7 IR spectrum for Estradiol Patch 24 hours after opening

Table 3 IR spectrum analysis for Estradiol

Corresponding Wavenumbers	
2916	C-H Stretching || Alkane
2848	C-H Stretching || Alkane or Aldehyde
1738	C=O Stretching || Esters (6-membered lactone)
1648	C=N Stretching || Imine / Oxime
	C=O Stretching || δ-lactam
	C=C Stretching || Alkene (Vinylidene)
1469	C-H Bending || Alkane (Methylene Group)
1435	O-H Bending || Carboxylic Acid
1371	C-H Bending || Alkane (Gem Dimethyl)
	O-H Bending || Alcohol
1237	C-O Stretching || Alkyl aryl ether
	C-N Stretching || Amine
1146	C-N Stretching || Amine
1019	C-O Stretching || Alkyl aryl ether
	C-N Stretching || Amine
958	C=C Bending || Alkene (disubstituted (trans))
935	?
798	C=C Bending || Alkene (trisubstituted)
719	C-H Bending || 1,3-disubstituted
608	C-Br Stretching|| halo compound
521	C-I Stretching || halo compound

Table 4 IR spectrum areas of interest for oxidation analysis for Estradiol Patch

2916	C-H Stretching	Alkane
2848	C-H Stretching	Alkane or Aldehyde
1738	C=O Stretching	Esters (6-membered lactone)
	C=N Stretching	Imine/Oxime
1648	C=O Stretching	d-lactam
	C=C Stretching	Alkene (Vinylidene)
1469	C-H Bending	Alkane (Methylene Group)
1435	O-H Bending	Carboxylic Acid
1371	C-H Bending	Alkane (Gem Dimethyl)
	O-H Bending	Alcohol
1237	C-O Stretching	Alkyl aryl ether
	C-N Stretching	Amine
1146	C-N Stretching	Amine
1019	C-O Stretching	Alkyle aryl ether
	C-N Stretching	Amine
958	C-C Bending	Alkene (disubstitued (trans))
798	C=C Bending	Alkene (trisubstituted)
719	C-H Bending	1,3 disubstituted
608	C-Br Stretching	halo compound
521	C-I Stretching	halo compound

In order to evaluate the oxidation, the wavenumbers of interest were outlined. These wavenumbers correspond to C=O, C-O, and O-H bonds. The peak strengths and band widths of the highlighted wavenumbers were compared between the two IR Spectrum graphs. The result of the analysis drew attention to the regions found in Figure 8. Additionally, to directly compare the band width and peak intensities of the two IR Spectra, the graphs were overlaid. The overlaid graphs and highlighted regions of interest can be found in Figure 9.

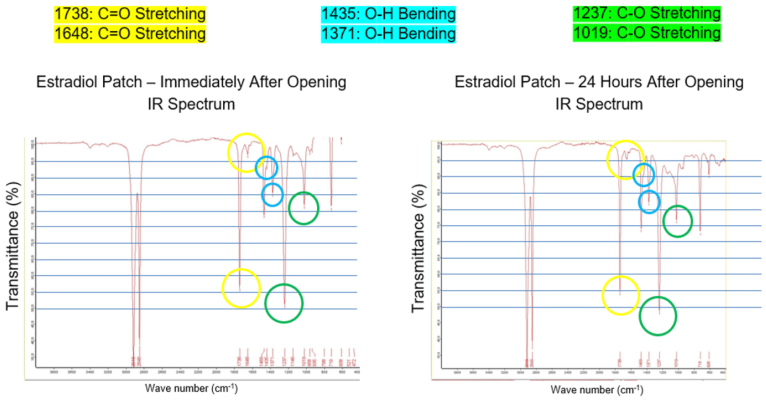

Figure 8 IR spectra comparison between Non-Oxidized and Oxidized Estradiol Patch samples

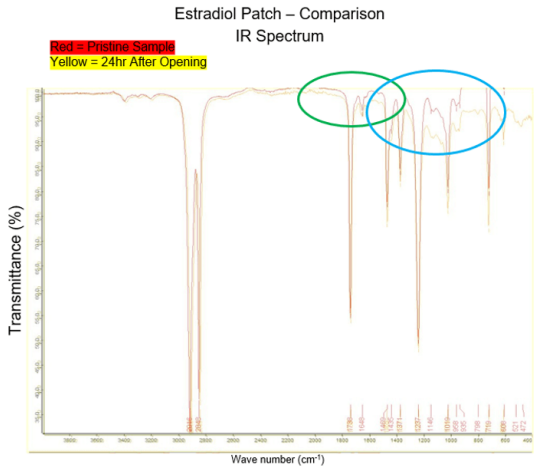

Figure 9 Estradiol Patch IR specta comparison: Oxidzied *vs.* Non-Oxidized.

4 Discussion

The IR Spectrum graph was successfully generated for the fresh Estradiol Patch sample. The graph was analyzed and the bonds corresponding to each wavenumber were identified. These bonds were compared to the chemical structure and formula for all the components in the sample. A detailed figure showing the components can be found in Figure 10. Comparison between the recorded bonds and the chemical structure of the components confirms that the bonds found through the IR Spectrometry correspond to the components.

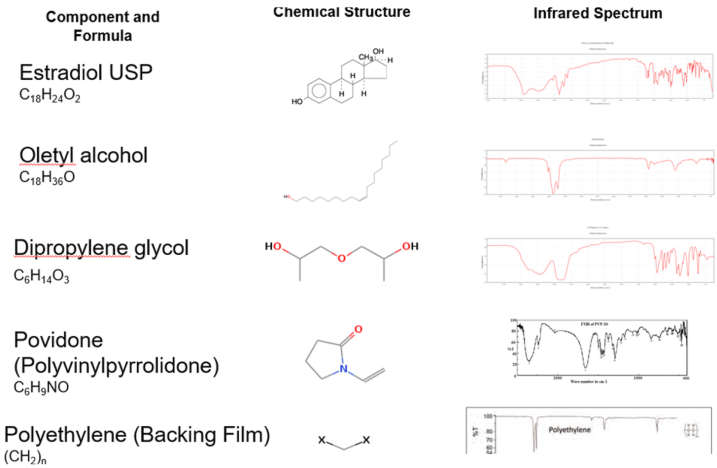

Figure 10 Chemical Formula and Structure for Components of Estradiol Patch [50–56]

It is important to consider the potential for the patch to undergo oxidation at ambient air conditions. For this test, we left the patch in ambient air for 24 hours and repeated the FTIR analysis. When investigating oxidation, the regions of interest are bonds that contain Oxygen, specifically the bonds C=O, C-O, and O-H. The effects of oxidation can either shorten or lengthen the peak at the corresponding wavenumber. Additionally, the band width (x-axis portion of the peak) will expand in some instances of oxidation. With that in mind, Figure 8 and 9 show the areas of interest that correspond to those criteria. At a wavenumber (cm^{-1}) of 1738 and 1648, the C=O bonds show evidence of a decreased transmittance (longer peak). At 1435 and 1371, the O-H bonds also show a decrease in transmittance and increase in peak length. At those wavelengths, the band width also increases. For 1237 and 1019, the C-O bonds show a decrease in transmittance and increase in peak length. At these wavelengths, the band width is significantly increased, and is evident in the overlaid image. Based on these results, it can be determined that oxidation does occur on a patch sample that is exposed to ambient air.

One of the long-term goals for this project is to identify chemicals or proteins in sweat that are responsible for causing patch failure. To do this, it is important to identify sweat biomarkers that are of interest in determining the presence of sweat on the patch. There are two major methods to lead to its identification: IR Spectroscopy and UV Spectroscopy.

Sweat has already been researched using IR Spectroscopy. Using IR Spectra Graphs generated by other researchers, useful bonds and regions can be identified for use in determining presence on the samples. Figure 11 contains an FTIR graph of sweat, and the wavenumbers relating to each peak are found in Table 5. Sweat often contains lactate as a dominant molecule. Lactate is known for strong signals in the wavenumbers of 1580 cm^{-1}, 1416 cm^{-1}, 1121 cm^{-1} and 1040cm^{-1}, which is shown in Figure 12 [57]. In addition, sweat exhibits a strong, broad signal around 3350-3400cm^{-1}, which is interesting because the Estradiol Patch does not contain any significant signals in this region, as evidenced by Figure 13. Since the Estradiol Patch does not have any bonds located in this region, it represents a prime candidate of sweat presence on used samples.

Table 5 IR Spectrum for Sweat - Peak Analysis [57]

3350	O-H Stretching	Intermolecular bonded Alcohol
	N-H Stretching	Secondary Amine
1580	C=C Stretching	Cyclic Alkene
1416	O-H Stretching	Carboxylic Acid
1121	C-O Stretching	Secondary Alcohol
1040	CO-O-CO Stretching	Anhydride

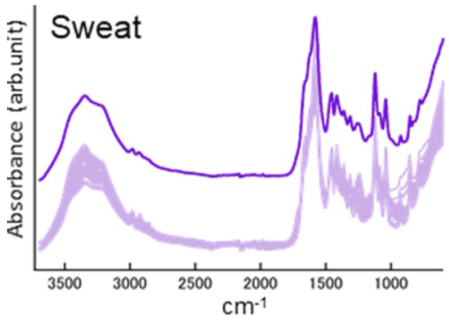

Figure 11 IR Spectrum for Sweat [57]

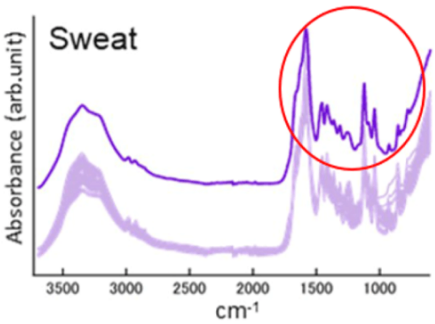

Figure 12 IR Spectrum for Sweat, Lactate region [57]

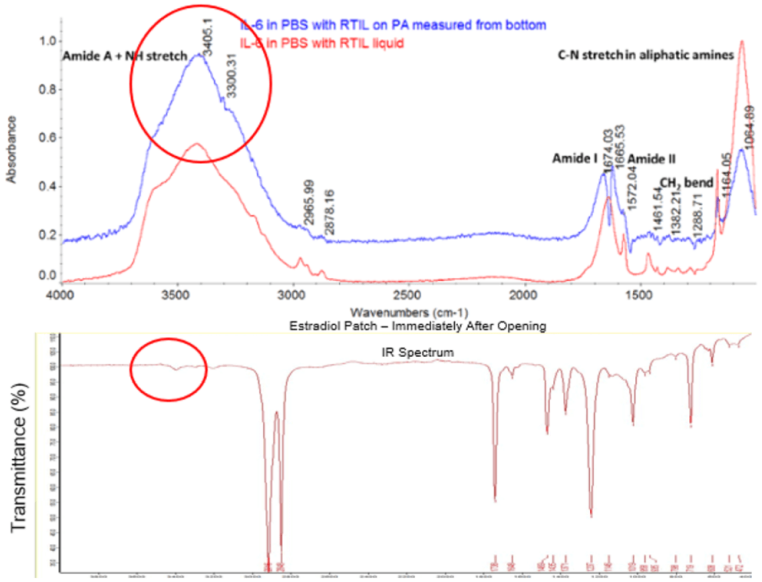

Figure 13 IR Spectrum of Sweat (Top) [59] compared to IR spectrum of Patch (Bottom) this study

The second method of identifying sweat biomarkers is the use of UV Spectroscopy. Sweat has been used extensively and is currently a very popular medium in the signal's world for the use of stress biomarkers. These biomarkers are naturally found in sweat and other bodily fluids, however when the body undergoes extreme stresses, the concentration drastically increases. This results in an increased peak on the UV Spectrum, and an example is shown for Cortisol and Dopamine in Figure 14. The most common stress biomarkers in Sweat are Cortisol, NPV, IL-6 and TNF alpha, found in Figure 15. Cortisol has the highest concentration. The presence of higher concentrations of these biomarkers in certain individuals may be a contributing factor to the failure of the adhesive patches. Due to that possibility, UV Spectroscopy would be beneficial in determining not only if sweat is present on the patch, but also if higher concentrations of

these stress biomarkers are related to patch failure.

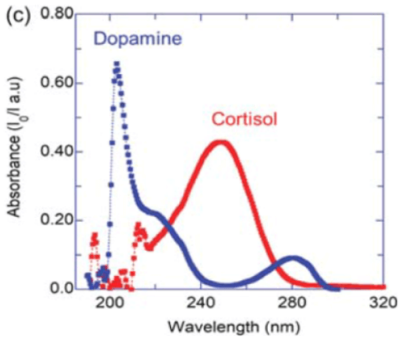

Figure 14 Example UV spectrum graph for Dopamine and Cortisol found in Sweat [65, 66]

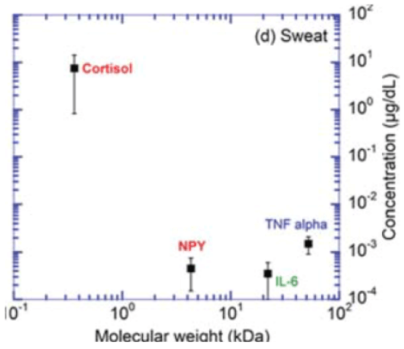

Figure 15 Stress biomarkers found in Sweat, plotted as Molecular Weight *vs.* Concentration [65, 66]

5 Conclusion

Our use of FTIR technique in this investigation of the Estradiol TDDS Patches identified spectrum comprising of numerous wavelengths indicating various bonds. The IR Spectrum for a pristine, unopened Estradiol patch was analyzed and the chemical bonds present were determined and compared to the known constituents of the patch. Additionally, it was determined that after a period of 24 hours, the Estradiol patch samples underwent oxidation when exposed to ambient air. Sweat biomarkers and identification techniques were also outlined in this work. Utilizing IR Spectroscopy and UV Spectroscopy, the presence of sweat on the Estradiol patch samples will be a competing mechanism influencing the adhesivity of the patch. Additionally, the biomarkers in sweat that are commonly used to identify intense stressors within the body represent an area of interest, as it is possible, they may have interactions with the adhesive of the patch which could lead to patch failure. In future works, additional patch samples will be collected and used for an extensive IR and UV analysis. By comparing the IR and UV Spectrum of "used" patches that did not fail, with "failed" patches, it may be possible to identify a cause for premature patch failure related to sweat interactions.

References

[1] Wokovich A, Prodduturi S, Doub W, *et al*. Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. European Journal of Pharmaceutics and Biopharmaceutics, 2006, **64**(1): 1-8. https://doi.org/10.1016/j.ejpb.2006.03.009

[2] Cilurzo F, Gennari G and Minghetti P. Adhesive properties: A critical issue in transdermal patch development. Expert Opinion on Drug Delivery, 2012, **1**: 33-45. https://doi.org/10.1517/17425247.2012.637107

[3] Urquhart J, Chandraskarane SK and Shaw JE. U.S. Patent No. US4031894A. Washington, DC: U.S. Patent and Trademark Office.

[4] Higgins JJ, Jagisch FC and Stucker NE. Butyl rubber and poly-isobutylene. In: Satas D, editor. Handbook of Pressure Sensitive Adhesive Technology II. Van Nostrand Reinhold, New York, 1989: 374-95.

[5] Auchter G, Aydin O, Zettl A, *et al*. Acrylic adhesives. In: Satas D, editor. Handbook of Pressure Sensitive Adhesive Technology III. Satas & Associates; Warwick, 1999, 396-456.

[6] Minghetti P, Cilurzo F, Pagani S, *et al*. Formulation Study of Oxybutynin Patches. Pharmaceutical Development and Technology, 2007, **12**(3): 239-246. https://doi.org/10.1080/10837450701212701

[7] Ulman K and Chilong L. Drug permeability of modified silicone polymers. III. Hydrophilic pressure-sensitive adhesives for transdermal controlled drug release applications. Journal of Controlled Release, 1989, **10**(3): 273-281. https://doi.org/10.1016/0168-3659(89)90077-1

[8] Cilurzo F and Tosi L. U.S. Patent No. US20060015077A1. Washington, DC: U.S. Patent and Trademark Office, 2003.

[9] Ginn M, Noyes C and Jungermann E. The contact angle of water on viable human skin. Journal of Colloid and Interface Science, 1968, **26**(2): 146-151. https://doi.org/10.1016/0021-9797(68)90306-8

[10] Maillard-Salin D. Physical evaluation of a new patch made of a progestomimetic in a silicone matrix. International Journal of Pharmaceutics, 2000, **199**(1): 29-38. https://doi.org/10.1016/s0378-5173(00)00357-4

[11] Minghetti P, Cilurzo F and Montanari L. Evaluation of Adhesive Properties of Patches Based on Acrylic Matrices. Drug Development and Industrial Pharmacy, 1999, **25**(1): 1-6. https://doi.org/10.1081/ddc-100102135

[12] Maillard-Salin D, Bécourt P and Couarraze G. A study of the adhesive–skin interface: Correlation between adhesion and passage of a drug. International Journal of Pharmaceutics, 2000, **200**(1): 121-126. https://doi.org/10.1016/s0378-5173(00)00369-0

[13] Wokovich AM, Shen M, Doub WH, *et al*. Evaluating elevated release liner adhesion of a transdermal drug delivery system (TDDS): A study of Daytrana™ methylphenidate transdermal system. Drug Development and Industrial Pharmacy, 2011, **37**(10): 1217-1224. https://doi.org/10.3109/03639045.2011.565773

[14] Suksaeree J, Prasomkij J, Panrat K, *et al*. Comparison of Pectin Layers for Nicotine Transdermal Patch Preparation. Advanced Pharmaceutical Bulletin, 2018, **8**(3): 401-410. https://doi.org/10.15171/apb.2018.047

[15] Rao S, Song Y, Peddie F, *et al*. A novel tri-layered buccal mucoadhesive patch for drug delivery: Assessment of nicotine delivery. Journal of Pharmacy and Pharmacology, 2011, **63**(6): 794-799. https://doi.org/10.1111/j.2042-7158.2011.01283.x

[16] Pongjanyakul T, Prakongpan S and Priprem A. Acrylic Matrix Type Nicotine Transdermal Patches: In Vitro Evaluations and Batch-to-Batch Uniformity. Drug Development and Industrial Pharmacy, 2003, **29**(8): 843-853. https://doi.org/10.1081/ddc-120024180

[17] Cilurzo F, Minghetti P, Pagani S, *et al*. Design and Characterization of an Adhesive Based on a Poly(Ethyl Acrylate, Methyl Methacrylate). AAPS PharmSciTech, 2008, **9**(3): 748-754. https://doi.org/10.1208/s12249-008-9102-4

[18] Ganti SS, Bhattaccharjee SA, Murnane KS, *et al*. Formulation and evaluation of 4-benzylpiperidine drug-in-adhesive matrix type transdermal patch. International Journal of Pharmaceutics, 2018, **550**(1-2): 71-78. https://doi.org/10.1016/j.ijpharm.2018.08.033

[19] Abu-Huwaij R, Obaidat RM, Sweidan K, *et al*. Formulation and In Vitro Evaluation of Xanthan Gum or Carbopol 934-Based Mucoadhesive Patches, Loaded with Nicotine. AAPS PharmSciTech, 2010, **12**(1): 21-27. https://doi.org/10.1208/s12249-010-9534-5

[20] Li Q, Wan X, Liu C, *et al*. Investigating the role of ion-pair strategy in regulating nicotine release from patch: Mechanistic insights based on intermolecular interaction and mobility of pressure sensitive adhesive. European Journal of Pharmaceutical Sciences, 2018, **119**: 102-111. https://doi.org/10.1016/j.ejps.2018.04.008

[21] Pichayakorn W, Suksaeree J, Boonme P, *et al*. Nicotine transdermal patches using polymeric natural rubber as the matrix controlling system: Effect of polymer and plasticizer blends. Journal of Membrane Science, 2012, **411-412**: 81-90. https://doi.org/10.1016/j.memsci.2012.04.017

[22] Rasmussen S, Horkan KH and Kotler M. Pharmacokinetic Evaluation of Two Nicotine Patches in Smokers. Clinical Pharmacology in Drug Development, 2018, **7**(5): 506-512. https://doi.org/10.1002/cpdd.431

[23] Minghetti P, Cilurzo F and Casiraghi A. Measuring Adhesive Performance in Transdermal Delivery Systems. American Journal of Drug Delivery, 2004, **2**(3): 193-206. https://doi.org/10.2165/00137696-200402030-00004

[24] Banerjee S, Chattopadhyay P, Ghosh A, *et al*. Aspect of adhesives in transdermal drug delivery systems. International Journal of Adhesion and Adhesives, 2014, **50**: 70-84. https://doi.org/10.1016/j.ijadhadh.2014.01.001

[25] Güngör S and Özsoy Y. Systemic delivery of antihypertensive drugs via skin. Therapeutic Delivery, 2012, **3**(9): 1101-1116. https://doi.org/10.4155/tde.12.87

[26] Akram R, Ahmad M, Abrar A, *et al*. Formulation design and development of matrix diffusion controlled transdermal drug delivery of glimepiride. Drug Design, Development and Therapy, 2018, **12**: 349-364.
https://doi.org/10.2147/dddt.s147082

[27] NDC 0781-7167 Estradiol Estradiol. (n.d.).
https://ndclist.com/ndc/0781-7167

[28] DailyMed - ESTRADIOL - estradiol patch, extended release. (n.d.).
https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm

[29] Markarian J. Manufacturing Considerations for Transdermal Delivery Systems. Pharmaceutical Technology, 2018, **42**(12): 40-42.

[30] Markarian J. Developing and Manufacturing Transdermal Patches. Pharmaceutical Technology, 2018, **42**(12): 41.

[31] Markarian J. Critical Parameters in Transdermal Patch Manufacturing. Pharmaceutical Technology 2017, **41**(12): 40.

[32] Platinum Partners & Gold Partners. (n.d.).
https://www.performancehealth.com/partners/iontopatch

[33] 3M Dow: A winning combination.
https://multimedia.3m.com

[34] Global transdermal drug delivery system tdds markets to 2023. (n.d.)
https://www.pharmiweb.com

[35] On-the-Go Patch Therapy.
http://www.iontopatch.com/device.html

[36] Party Patch Hangover Defense Transdermal Patch, Pack of 10. (n.d.).
https://www.zosanopharma.com

[37] Tapemark. (n.d.).
https://www.tapemark.com/blog

[38] Drug Delivery Systems. (n.d.).
https://www.3m.com/3M

[39] Zosano. (n.d.).
https://www.zosanopharma.com

[40] Clonidine Transdermal. (n.d.).
https://www.webmd.com/drugs

[41] Farahmand S and Maibach HI. Transdermal drug pharmacokinetics in man: Interindividual variability and partial prediction. International Journal of Pharmaceutics, 2019, **367**(1-2): 1-15.
https://doi.org/10.1016/j.ijpharm.2008.11.020

[42] Buskirk GA, Arsulowicz D, Basu P, *et al*. Passive Transdermal Systems Whitepaper Incorporating Current Chemistry, Manufacturing and Controls (CMC) Development Principles. AAPS PharmSciTech, 2012, **13**(1): 218-230.
https://doi.org/10.1208/s12249-011-9740-9

[43] Thermo Fisher Scientific. (2019, March 18). Confocal Raman Analysis of a Transdermal Nicotine Patch.
https://www.azom.com/article.aspx?ArticleID=15715

[44] Nicotine replacement therapy. (n.d.).
https://depts.washington.edu

[45] How to use transdermal patch. (n.d.).
https://www.healthline.com

[46] Drug Absorption, Drug Absorption, Distribution And Elimination: Pharmacokinetics. (n.d.).
https://www.columbia.edu

[47] Lin L and Wong H. Predicting Oral Drug Absorption: Mini Review on Physiologically-Based Pharmacokinetic Models. Pharmaceutics, 2017, **9**(4): 41.
https://doi.org/10.3390/pharmaceutics9040041

[48] Nicotine patch market report, 2017.
https://www.medgadget.com

[49] IR Spectrum Table & Chart. (n.d.).
https://www.sigmaaldrich.com

[50] Ethene, homopolymer. (n.d.).
https://webbook.nist.gov

[51] 1-vinyl-2-pyrrolidinone. (n.d.).
https://webbook.nist.gov/

[52] 9-Octadecen-1-ol, (Z). (n.d.).
https://webbook.nist.gov

[53] 2-Propanol, 1,1'-oxybis. (n.d.).
https://webbook.nist.gov

[54] Estradiol. (n.d.).
https://webbook.nist.gov

[55] Veeraiah, VAK. Synthesis and Characterisation of Poly (Vinylpyrrolidone) – Nickel (II) Complexes. IOSR Journal of Applied Chemistry, 2014, **7**(8): 61-66.
https://doi.org/10.9790/5736-07816166

[56] Elmer P. Polymer Analysis Solutions Compendium, 2016.

[57] Takamura A, Watanabe K, Akutsu T, *et al*. Soft and Robust Identification of Body Fluid Using Fourier Transform Infrared Spectroscopy and Chemometric Strategies for Forensic Analysis. Scientific Reports, 2018, **8**(1): 8459. https://doi.org/10.1038/s41598-018-26873-9

[58] Lactate. (n.d.). https://pubchem.ncbi.nlm.nih.gov

[59] Munje RD, Muthukumar S, Jagannath B, *et al*. A new paradigm in sweat based wearable diagnostics biosensors using Room Temperature Ionic Liquids (RTILs). Scientific Reports, 2017, **7**(1); 1950. https://doi.org/10.1038/s41598-017-02133-0

[60] Peel Adhesion of Pressure Sensitive Tape, 2019. httpS://www.pstc.org/files/public/101.pdf

[61] Shear Adhesion of Pressure Sensitive Tape, 2019. httpS://psatape.com.tw/pstc/pstc107.pdf

[62] Relative Performance of Release Coatings, 2019. http://psatape.com.tw/pstc/pstc16.pdf

[63] Tack Rolling Ball, 2019. http://psatape.com.tw/pstc/pstc6.pdf

[64] Loop Tack, 2019. http://psatape.com.tw/pstc/pstc16.pdf

[65] Steckl AJ and Ray P. Stress Biomarkers in Biological Fluids and Their Point-of-Use Detection. ACS Sensors, 2018, **3**(10): 2025-2044. https://doi.org/10.1021/acssensors.8b00726

[66] Ray P and Steckl AJ. Label-Free Optical Detection of Multiple Biomarkers in Sweat, Plasma, Urine, and Saliva. ACS Sensors, 2019, **4**(5): 1346-1357. https://doi.org/10.1021/acssensors.9b00301