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Review article

Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute

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Abstract

Transdermal drug delivery systems (TDDS), also known as ''patches,'' are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. In the Drug Quality Reporting System (DQRS), the United States Food and Drug Administration (FDA) has received numerous reports of ''adhesion lacking'' for transdermal drug delivery systems. This article provides an overview of types of transdermals, their anatomy, the role of adhesion, the possible adhesion failure modes and how adhesion can be measured. Excerpts from FDA reports on the lack of adhesion of transdermal system products are presented. Pros and cons of in vitro techniques, such as peel adhesion, tack and shear strength, in vivo techniques used to evaluate adhesive properties are discussed. To see a decrease in ''adhesion lacking'' reports, adhesion needs to become an important design parameter and suitable methods need to be available to assess quality and in vivo performance. This article provides a framework for further discussion and scientific work to improve transdermal adhesive performance. Published by Elsevier B.V.

Keywords: Transdermal drug delivery system; Transdermal system; Drug delivery; Patch; Adhesion; Tack; Peel; Shear

1. Introduction

Transdermal drug delivery systems (TDDS), also known as ''patches,'' are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. Several TDDS containing drugs such as clonidine, estradiol, fentanyl, nicotine, nitroglycerin, oxybutynin and scopoloamine are available in the United States. In the Drug Quality Reporting System (DQRS), the United States Food and Drug Administration (FDA) has received numerous reports of ''adhesion lacking'' for transdermal drug delivery systems (see Table 1).

The adhesive of the TDDS is critical to the safety, efficacy and quality of the product. To begin with, the therapeutic effect of the drug is linked to the adhesive performance of the TDDS. Reduction in the surface area of contact as a result of patch lift, or even the patch falling off, diminishes the delivery of drug from the patch. In other words, poor adhesion results in improper dosing of patients. Secondly, patches that fail to adhere for their prescribed time period must be replaced more often, thereby increasing the patient's cost. Thirdly, lack of adhesion is a safety issue. There is potential accidental dosing of children who may pick up fallen patches. Death and other serious medical problems have occurred when accidentally exposed to certain patches (e.g. transfer of a patch from an adult to a child while hugging, accidentally sitting or lying on a patch) [1,2]. Many prescribing information sheets for TDDS state that adhesion has not been studied. This article provides an overview of the significance of the adhesive

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Table 1
Excerpts from some reports that the FDA has received for "adhesion lacking" of TDDS

Reports about environmental condition use failure
- Heat, cold, sweating (perspiring) and showering prevent the patch from sticking to the surface of the skin for more than one day. A new patch has to be applied daily.
- The patches fall off during bathing and sleeping. ... has resorted to using medical tape to help secure patches. ... feels he is not getting his money's worth from this product.
- Patches fall off completely during bathing or swimming; patches sometimes fall off during walking.
- Slight movement and sweating will cause patches not to stick.
- (Compared to a brand previously used), the patch is thicker and does 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.

Reports of tape usage in the event of patch falling off
- Unable to make the patches adhere after the first day. The reporter has given them various types of tape and bandages to use, but none have proven satisfactory The patients reported that the medication does indeed work well when sticking, but that does not last long.
- Patient complained that the patch would not stick to the skin. The patient was using scotch tape to try to keep the patch on.
- Adhesive not sticking. ... patient was told to use adhesive tape over patch by R.N.
- Patches will simply not stay on. Reporter called the pharmacy and they suggested covering the patch with an adhesive strip.
- A patient re ported that the patches were not sticking to her skin. The reporter had difficulty reaching the manufacturer. Eventually, he reached a representative who advised him to communicate several tips to the patient that may solve the problem. 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 adhere with no tricks.

Reports of patient cost increasing due to lack of TDDS adhesion
- Patch does not stay on. ... feels that for the money he is spending on this product he should not have to resort to spending more money and time to insure that the product stays on.
- The patches will not stick and repeatedly fall off. It is causing patients to increase the number of refills they are obtaining in a month.
- Customer informed to use adhesive tape to keep the patch on. The patches are quite expensive and this problem of them not sticking can become quite costly.

Reports of loss of efficacy
- Does not consider the effectiveness of these patches to be as advertised for the reason that the therapeutic effect is degraded due to unreliable adhesive properties.
- Patient had been on product for about 1 year with no complications. Upon refilling prescription, patient complained of loss of efficacy. Also, rash and itching at administration site. Upon applying new patch from a different lot efficacy returned.

Reports of adverse events
- Patches are not sticking and patient is experiencing redness, swelling and itching at patch site.
- Patch pulled skin away causing bleeding/inflammation. (A different) brand patch caused no such reaction.
- (Compared to a previous brand), the esthetics and the performance of the patch is not the same. These patches are much larger and thicker. The skin beneath the patch was abraded and wet to the touch. When removing the patch, skin adhered to it and left an open sore.
- Removal of the patch is very difficult. Tearing skin upon removal.
- The adhesive is so sticky that it can tear or irritate elderly patients' fragile skin. This has occurred on more than one occasion.

Reports of lack of quality
- The adhesive sticks excessively to the clear plastic backing (release liner) and resulted in tearing of the patch and removal of significant adhesive.
- RN. reported that patch could not be removed from protective wrapper to apply to patient's skin.
- Patch would not flex with the patient's skin and therefore come off. The patches would not stay on the skin when they were re-applied.
- The customer feels the patches are too stiff and do not conform to the body.
- Patches wrinkle and fall off easily.
- It (the patch) does not stay on the skin very well. The patch is specifically not adhering around the outside edges. It 'gaps up' or 'tents up.'
- Within 24 h the patch began to curl at the edges and fall off.
- The look/feel/smell of the two different lot numbers were definitely not the same.
- There are small crystals on three patches.
- Residents (patients) complained about feeling of adhesive going on and coming off.
- Patient returned medication stating he had used these patches for more than 1 year and is familiar with them. He claims that these patches had more adhesive on them than usual causing difficulty in removing, more redness on skin area than usual.

Reports of safety concerns
- 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, then fell into her food.
- Transdermal systems are coming off the patients; finding them in their beds, in their hair, etc.
- Complaints from nurses regarding this product. The patches are falling off and are being lost in the linen.

in a transdermal drug delivery system and the necessity for adhesion testing.

2. Types of TDDS

Broadly speaking, most commercially available TDDS (e.g. Catapres-TTS®, Climara®, Climara Pro®, Combipatch®, Duragesic®, Menostar®, Ortho Evra®, Oxytrol®, Transderm Scop®, Vivelle®, Vivelle-Dot®) can be categorized as reservoir systems, matrix systems without a rate-controlling membrane or matrix systems with a rate-controlling membrane (see Fig. 1). Reservoir systems consist of three major components: the drug reservoir, the rate-controlling membrane and the

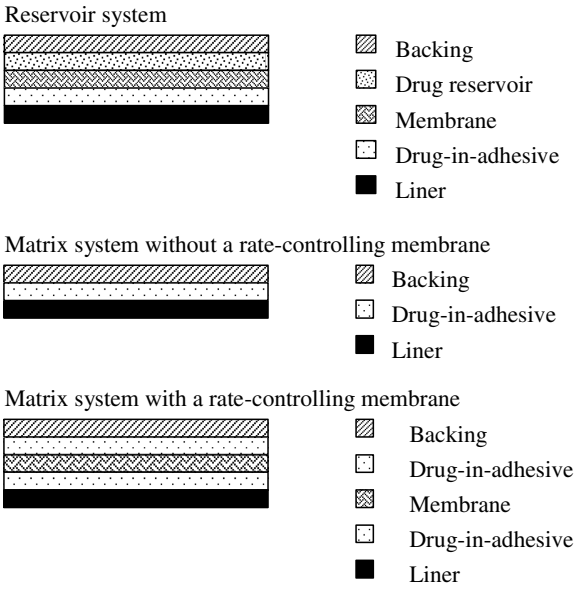


Fig. 1. Types of transdermal drug delivery systems.

adhesive. Typically, the drug reservoir contains the drug and excipients. The drug permeates through the membrane and the adhesive to reach the skin. The adhesive component of the TDDS responsible for skin adhesion either may completely cover the drug release area (continuous adhesive) or may form a perimeter around a non-adhering drug release surface (peripheral adhesive). In a matrix system, the drug is in the adhesive. The adhesive performs the roles of formulation foundation and adhesive. In matrix systems with a rate-controlling membrane, the matrix system contains a membrane between the drug-in-adhesive layers.

3. Anatomy of a TDDS

3.1. Release liner

During storage the patch is covered by a protective liner that is removed and discarded before the application of the patch to the skin. Since the liner is in intimate contact with the TDDS, the liner should be chemically inert.

3.2. Backing

Backings are chosen for appearance, flexibility and need for occlusion. Examples of backings are polyester film, polyethylene film and polyolefin film. Other considerations are the backing additives leaching out and diffusion of excipients, drug or enhancer through the backing. An overemphasis on the chemical resistance often may lead to stiffness and high occlusivity to moisture vapor and air, which cause the TDDS to lift and possibly irritate the skin during long-term wear.

3.3. Overlay

A TDDS may include a drug-free adhesive coated film, foam or nonwoven component designed to be placed over a transdermal patch that has been applied onto the skin. This overlay secures the medicated patch to the skin of the patient [3]. Some TDDS manufacturers, TDDS distributors or medical personnel might suggest placing adhesive tape over the patch if the patch lifts or even falls off. The effect of this additional occlusivity has on drug delivery and skin irritation may not have been studied.

3.4. Membrane

A membrane may be sealed to the backing to form a pocket to enclose the drug-containing matrix or used as a single layer in the patch construction. The diffusion properties of the membrane are used to control availability of the drug and/or excipients to the skin.

3.5. Enhancer and excipients

An enhancer (e.g. propylene glycol, methyl laurate, ethyl oleate, carvone, lauric acid, oleic acid, *N*-methyl-pyrrolidone, azone, isopropyl myristate, alcohol) may modulate the skin permeability in some fashion [4–6].

3.6. Pressure sensitive adhesive

An approach to explain the adhesive properties of pressure sensitive adhesives (PSAs) is based on the belief that the PSA will adhere to a substrate, in this case skin, because of interatomic and intermolecular attractive forces established at the interface, provided that intimate contact is achieved [7,8]. To obtain this degree of contact, the material must be able to deform under slight pressure, giving rise to the term "pressure sensitive." Adhesion involves a liquid-like flow resulting in wetting of the skin surface upon the application of pressure, and when pressure is removed, the adhesive sets in that state. A PSA wets and spreads onto skin when its surface energy is less than that of skin [8]. After the initial adhesion, the PSA/skin bond can be built by stronger interactions (e.g. hydrogen bonding), which will depend on skin characteristics and other parameters.

Widely used PSA polymers in TDDS are polyisobutylene (PIB)-based adhesives, acrylics and silicone-based PSAs. The PSA can be used to affix the TDDS to the skin and/or as a carrier for the drug. The PSA can be located around the edge of the TDDS or be laminated as a continuous adhesive layer on the TDDS surface [9]. The PSA should be compatible with the drug and excipients since their presence can modify the mechanical characteristics of the PSA and the drug delivery rate. When selecting a PSA for a TDDS, several properties need to be evaluated that may influence adhesive performance: solubility of drug and excipients; effect of dissolved/dispersed additives on

adhesion; long-term stability of dissolved/dispersed components; compatibility of the backing layer and release liner with these components; application period; effect of moisture [5,9–11]. An ideal requirement of a TDDS adhesive is that it should be nonirritating and nonsensitizing to the skin, adhere to varying skin types, adhere strongly to the skin for the prescribed application period, be easily removable without trauma, leave no residue on the skin upon removal and be comfortable to wear [12].

4. Role of adhesion in drug delivery

Adhesion or the lack of adhesion of transdermal systems to the skin is a critical factor directly related to drug delivery and therapeutic effect. Since the drug absorption process is related to the drug partition between the TDDS and the skin and the drug permeation process, complete skin contact over the entire delivery surface for the entire label application period is essential. If the TDDS lifts or partially detaches, the effective area of TDDS/skin contact, and thus the drug absorption, changes in an unpredictable manner. Therapeutic failure can then occur. Only a constant TDDS/skin contact over the whole application period allows a consistent delivery and absorption of the drug [7,13]. In other words, the quality of contact between patch and skin is directly reflected in the consistency of drug delivery.

Absorption of drug through the skin is affected by a number of factors such as skin sites, skin thickness, skin temperature, body temperature, blood flow, lipid concentration, number of hair follicles, skin cleansing, hydration status, sweat gland function, ethnic group, pH of skin surface and the state and integrity of the stratum corneum [9,14–20]. Occlusion can change the hydration and temperature of the skin [20]. Average skin thickness varies as a function of age, gender and race [15]. For thinner skin, serum drug concentrations may increase. Also, if a TDDS is applied to compromised skin, serum drug concentrations may increase [15]. Aged skin has lower moisture content and is less elastic, while younger skin is more hydrated and consequently more elastic [8].

For an adhesive to adhere to a substrate, a fundamental thermodynamic requirement has to be satisfied: the measured surface energy of the adhesive must be equal to or less than that of the adherend (e.g. human skin). Ginn et al. [21] reported that the surface energy of clean, dry human skin is about 27 dyn/cm and that this value increased when the surface energy was measured on dirty or unwashed skin. Wet or unclean skin may be thought of as being more hydrophilic (having higher surface energy) and clean and dry skin as mostly lipophilic (lower surface energy). Kenney et al. [22] showed that the surface energy of in vivo human skin increases with humidity and temperature. Therefore, the surface energy of the TDDS should be less than the lowest critical surface energy value reported for the skin (27 dyn/cm). This is a necessary but not sufficient condition for adhesion. The other requirements for adhesion are kinetic in nature, involving wetting rates and viscoelasticity of the adhesive.

An increase in adhesion after TDDS application can be related to the viscoelastic flow of the adhesive as it warms to skin temperature. As the adhesive flows over the skin surface, the adhesive/bond increases and then plateaus as the temperatures of the adhesive and of the skin equalize. Hydration of the skin and subsequent swelling of the stratum corneum result from occlusive products which tend to weaken the cohesive strength of the stratum corneum [23]. The force required to remove a TDDS may decrease because of reduced adhesive contact, diminished drug concentration and a gradual sloughing of the outermost layers of the stratum corneum.

5. Modes of failure in TDDS

Removal of the TDDS from a substrate (e.g. skin) involves the work done in the extension of the adhesive, in the distortion of the backing during the stripping action and in the separation of the adhesive/surface interface. When a TDDS is peeled away from a substrate, it can debond via different modes of failure. When the patch is peeled, it is expected that it will strip cleanly from the skin, leaving no visible residue [24]; this type of failure is an adhesive failure, Case I. If the adhesive transfers to the skin, leaving no adhesive on the TDDS, this type of failure is an adhesive failure, Case II. Cohesive failure, Case III, is indicated when adhesive is left on the TDDS and on the skin. These modes are illustrated in Fig. 2. Case IV is a

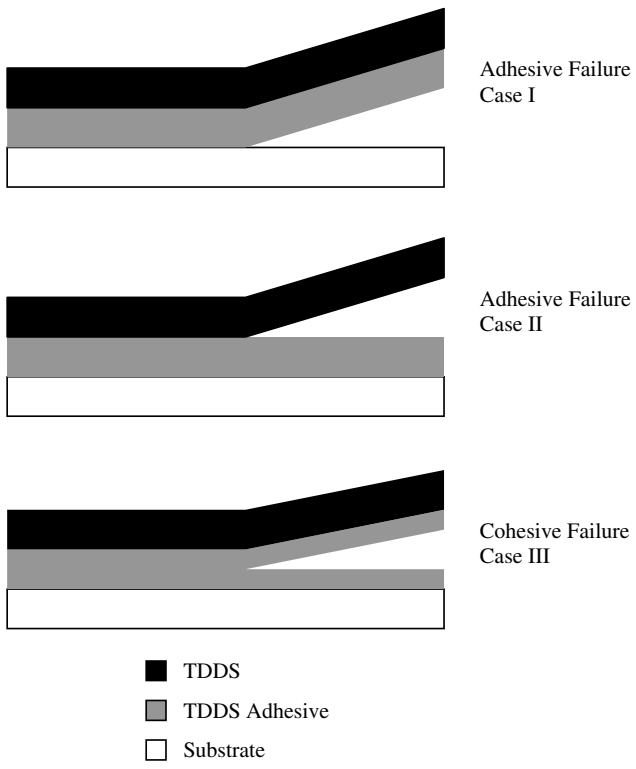


Fig. 2. Diagram of adhesive failures and cohesive failure.

combination of adhesive and cohesive failure. Failures other than Case I may be considered as a sign of a flawed transdermal drug delivery system. Based on the type of failure mode, it may be possible to identify potential causes of the failure.

6. Techniques to measure adhesive properties

The adhesive performance of TDDS is a critical factor determining its drug delivery, therapeutic effect and patient compliance. Several in vitro techniques have been used to monitor adhesive performance such as peel adhesion, tack and shear strength. However, these tests were developed for industrial pressure sensitive tapes (see Table 2). Peel adhesion, tack and shear measurements are not true material properties of the adhesive since they depend on substrate, backing material and test parameters. The following points should be considered when developing adhesive tests for TDDS: the methods developed should assure lot-to-lot quality for the product; the methods should be stability indicating; the methods should be sufficiently discriminating to detect changes that may influence product performance; the methods should be reproducible.

It is essential to test the adhesive properties of the TDDS in its final form to ensure acceptable adhesive quality. The evaluation of the PSA in bulk, even if the effects of the active ingredient and other excipients are studied, is not sufficient to predict the adhesive performance of the TDDS. Causes of instability such as the drug and excipient undergoing phase changes (e.g. dissolved drug may crystallize, dispersed drug may agglomerate) could adversely affect adhesive properties [25]. Adhesive customization is important in product development. Adhesive properties can be influenced by the type and concentration of additives used for improving the adhesion properties, the thickness of the adhesive, the type and concentration of the drug loaded, the type and concentration of enhancers, the composition and thickness of the backing layer and the solvent residue [7,9,13,24,26–31].

6.1. Peel adhesion

Peel adhesion measures the force required to peel away an adhesive once it has been attached to a surface. Most currently used test methods for TDDS peel adhesion are based on methods developed for industrial tapes. These typically call for the use of a stainless steel test panel as the substrate, peel angles of 90° or 180°, cutting the sample into an exact width, dwell times of one minute and a peel speed of 300 mm/min. The peel adhesion measurement is greatly influenced by the experimental parameters such as dwell time, substrate (e.g. stainless steel, skin, HDPE), peel angle, peel speed, etc. [24,32]. The measurement also depends on the TDDS backing and adhesive thickness [7,9,24].

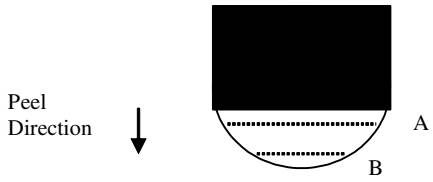
There are several complications with measuring in vitro peel adhesion. To begin with, cutting the TDDS to measure peel adhesion can be difficult. Industrial tape methods PSTC 101 and ASTM D3330 [33,34] call for cutting the sample into an exact 1 or 1/2 in. wide strip using a specimen cutter. This is simple for transdermal systems that are of the matrix type. However, TDDS that are of the reservoir type may "leak" when cut; therefore, reservoir systems may need to be ran "as-is." Secondly, the type of test panel and stretching of the patch backing will affect peel adhesion. The typical test panel, stainless steel, has a surface energy that is quite different from that of human skin (500 and 27 dyn/cm, respectively); the strength of the bond established between the TDDS and the stainless steel test panel may be greater than the tensile strength of the TDDS backing. For example, when a transdermal system is peeled from human skin, no backing deformation may be visible; however, when the transdermal system is peeled from stainless steel, significant stretching and deformation of the patch may be seen. When this occurs, the peel adhesion test is not a true indication of the real nature of the adhesive bond. A substrate that is similar to human skin needs to be chosen.

Calculating peel adhesion can be difficult. Peel adhesion is the force per unit width required to break the bond between an adhesive and the substrate (e.g. stainless steel) when the sample is peeled back at a controlled angle (e.g. 90°) at a standard rate (e.g. 300 mm/min) [33,34]. In other words, peel values are reported in force per unit of width (e.g. g/cm). The value for peel adhesion is independent of length but is dependent upon the width of the sample [33,34]. For those samples that were cut into an exact 1 or 1/2 in. wide strip using a specimen cutter, peel adhesion is easily calculated since the width is uniform throughout. However, a patch that does not have the same width throughout is more complex. For example, for a circular patch that is not cut into an exact 1 or 1/2 in. wide strip, the width is changing continuously as it is being pulled (see Fig. 3). A suggestion for calculating the peel strength of a circular sample was offered through the Pressure Sensitive Tape Council. In pulling a circle, the chord length is continually decreasing. If the force data can be gathered as a function of time and related to the location of the chord, the force divided by the chord length should be somewhat constant, and the average value could be used as the measure of peel strength.

Table 2
Performance related tests for industrial pressure sensitive tapes

PSTC[a] 101: Peel adhesion of pressure sensitive tape
ASTM[b] D3330: Standard test method for peel adhesion of pressure-sensitive tape
PSTC 107: Shear adhesion of pressure sensitive tape
ASTMD3654: Shear adhesion of pressure sensitive tape
ASTM D2976: Pressure sensitive tack of adhesives using an inverted probe machine

[a] PSTC: Pressure Sensitive Tape Council.
[b] ASTM: American Society for Testing and Materials.



The width at point "A" is not the same as the width at point "B." Therefore, point "A" will have a different force compared to point "B."

Fig. 3. Width of circular sample changing as it is being pulled.

6.2. Tack

The tack of an adhesive was initially evaluated by a highly subjective "thumb test" (i.e. touching the surface of the adhesive with the thumb and sensing the force required to break the bond). The probe tack test was developed in an attempt to simulate and refine the thumb test [28]. For a probe tack test, a probe touches the adhesive surface with a light pressure, and the force required to break the bond after a short period of contact is measured. With some tack instruments (e.g. Texture Analyzer), not only can the peak force at separation be measured, but also the area under the curve, the presence and magnitude of a shoulder in the curve and the displacement upon de-bonding [28]. Rather than use the maximum force experienced during the bond separation as the indication of tack, Zosel has suggested that the tack energy as represented by the area under the curve correlates best with the thumb tack test [28]. Tack is not simply a function of the material properties of the adhesive but is greatly influenced by the experimental parameters. Tack depends on the contact area, the contact pressure, the time of contact (or dwell time), rate of separation and the test environment [28]. As with peel adhesion testing, tack is relative to both the substrate material (e.g. stainless steel) and the sample adhesive.

6.3. Shear adhesion

Shear strength or creep compliance is thought of as a measure of the cohesive strength. This is a viscoelastic measurement that can be related to performance and processing. High creep compliance indicates a low cohesion. This can be observed by the TDDS oozing or leaving adhesive residues on the TDDS outer edges, liner or pouch [35]. Some TDDS may contain a protective film above and below the patch that is discarded at the time of use (e.g., a protective film over the backing and a protective film over the release liner). The adhesive residues from the cold flow or "creeping" of the TDDS may also contain drug if the system is a type that contains drug in the adhesive. The cold flow may also make it difficult for the patient to remove the TDDS from the pouch or make it difficult for the patient to remove the TDDS from the protective film or the release liner. A low creep compliance is desirable; however, too low of a value leads to loss of tack and peel adhesion. The adhesive must exhibit an elastic cohesiveness and a resistance to flow under stress. Even though the cold flow or creep observation is subjective, the analyst should record any TDDS oozing or adhesive residues on the TDDS outer edges, protective film or pouch after manufacturing and at stability testing intervals.

There are two categories of shear testing-dynamic and static [36,37]. In the dynamic test, the TDDS is pulled from the test panel at a constant speed. Dwell time, speed, type of test panel, mode of failure and sample size should be noted, and the maximum force per unit width required to remove the TDDS from a specified area is usually reported. The relationship between shear force and test area is curvilinear; the standard deviation increases with the width of the sample [37]. In the static test, the TDDS sample is applied to a test panel that is at an angle 2° from the vertical, and the sample is subjected to a shearing force by a means of a given weight (e.g. 1000 g) suspended from the TDDS. Dwell time, weight used, type of test panel, mode of failure and sample size should be noted; the time taken for the TDDS sample to detach from the test panel is reported. One complication of shear testing is the stretching of the sample as it is being pulled. As with peel adhesion, industrial tape methods call for the use of a stainless steel test panel, but a substrate that is similar to human skin needs to be chosen. When the transdermal system is pulled from stainless steel, considerable stretching and deformation of the transdermal system may be seen. Some methods call for reinforcing the transdermal system by applying tape to the patch backing.

6.4. In vivo

An in vitro peel adhesion test that predicts adhesion to human skin has not been developed. Skin is a variable material, and the test panels and probes used for testing adhesion properties are poor models of skin. The lack of in vivo/in vitro correlation may be attributed to the differences in the surface energy between the TDDS and skin versus the TDDS and a stainless steel test panel. The surface energy of clean skin (27 dyn/cm) is lower than those of stainless steel (500 dyn/cm), polyethylene (31 dyn/ cm), polymethacrylate (39 dyn/cm) and polystyrene (33 dyn/cm) [28]. In addition, the test panels and probes used for in vitro testing do not take into account different skin types, skin oils, motion and changing moisture levels. Skin is rough while stainless steel is smooth, and skin is flexible while stainless steel is stiff. When a TDDS is removed from the skin, considerable skin deformation can be seen as a result of its extension [38]. Therefore, when a peel test is performed using the skin as a substrate, the work expended in the TDDS detachment includes the deformation of the skin itself as well as separation of the TDDS from the surface [10,32].

There is a lack of evidence for a relationship between the results obtained in in vitro adhesion tests and the in vivo adhesion performance of TDDS [13]. The in vitro

Table 3
Scoring system for a TDDS

0 = 90% adhered (essentially no lift off of the skin)
1 = 75% to <90% adhered (some edges only lifting off of the skin)
2 = 50% to <75% adhered (less than half of the system lifting off of the skin)
3 = <50% adhered but not detached (more than half the system lifting off of the skin without falling off)
4 = patch detached (patch completely off the skin)

conditions do not necessarily represent the performance of the TDDS under in vivo conditions. Skin is subject to moisture: either internal (perspiration) or external (washing), conditions that are difficult to duplicate for in vitro testing [39,9]. In addition, in vivo moisture conditions are greatly influenced by environmental factors such as heat, humidity and exercise. Changes to these factors may be caused by common activities such as bathing, showering, sunbathing, sauna, whirlpool, dressing, light exercise, strenuous exercise that produces a heavy sweat and swimming [40]. It should not be unreasonable to expect a TDDS to adhere for the label application period. Also, it should not be unreasonable to expect a TDDS with a label application period of 3 or more days to adhere during showering or bathing.

Currently, in vivo adhesion performance is usually based upon subjective observations. The performance may be estimated by a scoring system based on patch lift (see Table 3) [41–43]. Adhesion to skin is scored from 0 to 4, in which 0 indicates that the patch did not lift and 4 indicates that the patch fell of the skin. The condition of the skin before application of the TDDS is usually not stated.

7. Conclusions

Currently, many of the clinical trials utilize placebo patches to determine the adhesion performance of new drug products [41,42,44,45]. Use of placebo patches cannot be justified because the type and concentration of the drug, the compatibility of the drug with the TDDS components and the compatibility of the drug with the excipients may have an effect on the adhesive properties of the TDDS. Some patient instructions allow for taping of the edges of a patch that is lifting. It seems unreasonable to expect the patch to fall off (or to allow the manufacturer to expect the patch to fall off), and, therefore, the adhesion characteristics of the finished product must be designed to provide the patient with complete and consistent adhesion over the entire application period.

Novel dosage forms are often developed to target delivery of drugs, improve compliance and ease for patients and reduce toxicity. For the more common dosage forms (e.g. tablets, injectables, oral solutions), a host of direct and/or surrogate measurement techniques exist. However, new dosage forms typically require development of new analytical techniques for their characterization. The methods developed should be stability indicating, assure lot-to-lot consistency and product performance and be reproducible. TDDS are a novel dosage form which relies on good adhesion over a period of many hours or days to ensure proper drug delivery. Skin adhesion is one of the most important functional properties for a TDDS. Poor adhesion results in improper dosing of patients and potential accidental dosing of children who may pick up fallen patches. Consistent methodology to test the adhesion properties of TDDS and ensure their safety does not exist. Although in vivo human skin testing is the most reliable method for evaluation of TDDS, the time, safety and money involved in human trials prohibit the extensive use of in vivo testing methods. Therefore, it is important to develop in vitro adhesion testing methodology. It is desirable that the outcome of an in vitro adhesion test correlates with in vivo skin adhesion. To keep health care costs manageable, methods also need to be adequate to compare the adhesion properties of a generic transdermal drug delivery system to the adhesion properties of an innovator transdermal drug delivery system.

The adhesion of a TDDS needs to be part of the upfront design of the product. Without understood, reproducible in vitro test methods, assessing the effect of formulation and manufacturing changes on adhesion will not be possible. Once adhesion becomes an important design parameter and suitable methods are available and understood, the FDA should see a decrease in ''adhesion lacking'' reports. Until then, a scientific work in this area needs to continue.

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