Prototype Development and Clinical Testing of a Temperature-Sensitive High-Adhesion Medical Tape to Reduce Medical-Adhesive Related Skin Injury and Improve Quality of Care

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Abstract

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Medical adhesives are used to secure wound care dressings and critical devices to the skin. Without means for safe removal, these strong adhesives are difficult to painlessly remove from the skin, and often result in medical adhesive related skin injuries (MARSI), which can take weeks to heal and increase the risk of infection. Alternatively, to avoid MARSI, lower adhesion medical tapes are chosen, leading to device dislodgement and further medical complications. ThermoTape is a high adhesion medical tape designed for low skin trauma upon release. By warming the skin-attached tape prior to removal, a significant loss in adhesion is achieved, allowing for more rapid, painless, and injury-free removal. A C14/C18 acrylate copolymer was developed and combined with a selected pressure sensitive adhesive material. This formulation was applied as a wet film on a thin backing substrate and heated to remove solvents. The addition of 1% C14/C18 acrylate copolymer yielded the largest temperature responsive

drop in adhesion to a surface and was further refined by control of film drying times and temperature. The adhesive film was characterized with AFM, where distinct nanodomains were identified on the exterior surface of the pressure sensitive adhesive. After heating above the melting point of the additive, these nanodomains contribute to a reduction in the adhesive peel force perhaps by weakening the adhesive-substrate boundary layer. ThermoTape was clinically tested in a 53-subject comparative single-blind clinical trial. ThermoTape was benchmarked with Tegaderm™ (high adhesion) and Kind Removal Tape (KRT- low adhesion). All three tapes were applied to both the left and right forearm and were removed 24 hours later, the right arm without heat and the left arm by directly applying a heat pack for 30 seconds. There were clinically and statistically significant results supporting reduced pain of ThermoTape with warming, with an average of 58% decrease in pain, which is paired with a statistically significant 45% reduction in skin redness. In contrast, there were statistically insignificant differences in pain and redness for Tegaderm™ and KRT with warming. These results provide compelling evidence that warming ThermoTape prior to removal can reduce pain and injury when compared to standard medical tapes. This could allow for stronger attachment of wound care dressings and critical medical devices while reducing the cases of MARSI. Two ThermoTape prototypes were fabricated with two different PSA thicknesses, representing two different use cases, and demonstrating the tunability of the ThermoTape system. Increasing the thickness enabled a higher peel force at 25ºC, accompanied by a release similar to KRT. Several pilot studies were conducted to further refine the design, demonstrate long-term wear, test different PSA thicknesses,

and to prepare for clinical testing at Harborview Medical Center. A manufacturing plan was developed to transition ThermoTape from the lab to high volume manufacturing.

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Chapter 1: Introduction

1.1 Medical Adhesives

1.1.1 Overview

Medical adhesive tapes are an integral part of healthcare delivery and are used in all care settings to cover and secure wound dressings or critical medical devices to the skin, such as intravenous (IV) lines [1]. All medical tapes consist of a pressure-sensitive adhesive (PSA) applied to a plastic or fabric backing that function as a carrier for the adhesive, providing structural and protective properties [2]. The combination of backing and adhesive determines the characteristics of the tape and informs nurses' decisions in the selection of the appropriate tape for the patient given the specific task required [3]. For instance, silicone-based adhesives such as 3M™'s Kind Removal Tape (KRT), generally have lower adhesion; and acrylic adhesives such as 3M™'s Durapore™ and Tegaderm™, generally have higher adhesion [3,4].

1.2 Clinical Problem

1.2.1 MARSI

Although effective and easy to apply, the adhesion of high adhesion tapes can increase over time, leading to a painful and time-consuming removal process that may ultimately result in tape-induced injuries [3]. Long-term skin contact or repeated removal of high adhesion tapes from the same location on the body can lead to painful and time-consuming removal processes which are correlated to Medical-Adhesive Related Skin

Injuries (MARSI) [2]. Further, many younger patients will vividly recall removal of tape and adhesives as one of the most negative memories related to medical procedures.

MARSI is defined as “erythema and/or other manifestations of cutaneous abnormality that persists 30 min or more after the removal of the adhesive” [2]. These injuries often occur during tape removal and include skin tears, blisters, and stripping of the skin [4]. These injuries cause pain and discomfort and can increase the risk of infections, increase wound size, and delay wound healing [4]. All these morbidities can increase medical costs, negatively impact patient safety, and lead to lower patient satisfaction [5]. MARSI is prevalent, but it is known to be underreported [4]. Prevalence rates vary between studies. One study reported as high as 13% in the general population, with 98.6% of nurses considering skin tears common or very common [6,7]. A cross-sectional, multiple-center epidemiological study performed on 697 adults aged from 18-89 showed a MARSI prevalence rate of 19.7%, noting that the risk increased for patients over 50 years [8]. While MARSI can occur at any age, it is more common in the young and elderly, due to the fragility of their skin. Nurses in neonatal intensive care units and nursing homes considered skin tears “extremely common” [2,9]. Higher risks are borne by children fighting disease, which can make a skin tear and/or infection life-threatening. This is particularly important when the tape is applied and removed repeatedly at the same skin location, such as at an implanted central venous catheter. An observational study examining the occurrence of MARSI in a pediatric intensive care unit of critically ill children reported an incidence rate of over 50% [10]. In addition to causing significant pain, distress, and medical complications, the cost of MARSI on average is 24 minutes of extra time, added medical supplies, and an additional medical doctor’s visit in over 10% of

cases [11]. These effects illustrate both the additional health resources expended, and patient distress caused by MARSI.

1.2.2 Device Dislodgement

Low adhesion tapes are often used as an alternative to higher adhesion medical tapes to avoid MARSI [3]. However, these low-adhesion attachment tapes are associated with a higher risk of device dislodgement, which is classified as a medical error [2,12]. A comparative study of a low adhesion medical tape, 3M™ Kind Removal Tape (KRT), and standard acrylic-based medical tapes was conducted over a two-week period with the participation of 200 nurses [13]. Of the 29% of the nurses that did not prefer the lower adhesion tape, over 75% were dissatisfied with KRT due to unreliable adherence. Furthermore, silicone-based tapes adhere poorly to other silicone products and plastic tubing [2]. As such, KRT and similar low-adhesion tapes cannot be used to properly secure critical medical devices to the skin, which is essential for patient safety.

As a result, many nurses avoid low-adhesion medical tapes and are left with high adhesion medical tapes that carry the risk of MARSI during removal [3]. Even when nurses select high adhesion tapes, these can still lead to dressing or device dislodgement [3]. It has been reported that frequent and daily dislodgements occur, with 68% of respondents to a survey reporting often, daily, or multiple times daily occurrence [12]. For IV lines, the mean rate of dislodgement is 17.5%, with all these cases risking medical complications that would be classified as a medical error [14]. It was also found that dislodgement was responsible for 50% of all cases where an IV must be replaced [14]. The average cost for IV lines ranges between $28 to $35, though the actual cost is

dependent on the type of IV used, geographical location, and the other medical technologies used to support it [14]. When failure occurs, another IV is required, possibly leading to an extended hospital stay, an increase in treatment cost, and infection. IV placement is a painful experience, with no certainty that one attempt will obtain an adequate replacement. The most common source of pain in children in hospitals is procedural pain, and increased IV placement events will negatively impact the patient's experience [15]. A catheter-related blood stream infection (CR-BSI) results in an additional 7 to 20 days in a care facility, with additional costs of up to $56,000. The total annual cost of CR-BSI is $2.3 billion per year in US intensive care cases [14]. Wound care dressing dislodgements lead to an exposed wound, which can lead to infection and extended healing times. Many of these dislodgments occur with high adhesion medical tapes. The current design of medical tapes may be at their maximum adhesion levels as they already result in a high incidence of MARSI. From our 150+ stakeholder interviews we learned that nurses caring for children would prefer to have significantly higher skin adhesion to keep critical devices like IV lines and nasogastric tubes secure and maintain wound care dressings to prevent infection, reinjury, and other complications, but that their current high adhesion tapes still lead to regular dislodgement [16]. Nurses indicated that they must choose either high adhesion tapes which risks MARSI, or lower adhesion tapes and increase the risk of dislodgement.

1.3 Proposed Solution: ThermoTape

ThermoTape is a new high adhesion medical tape which is designed for low skin trauma upon release. ThermoTape is a temperature sensitive tape that reduces adhesion when

warmed to 43ºC, which is above febrile skin and below the skin pain threshold of 45ºC. ThermoTape incorporates a high adhesion commercially available base pressure sensitive adhesive (PSA) (Duro-Tak AH-115) and a custom patent protected temperature responsive polymer additive. While on skin, ThermoTape offers industry leading high adhesion levels. Upon removal, application of a heat pack significantly reduces ThermoTape adhesion, allowing for rapid and injury-free removal. The temperature response is achieved by the addition of a custom additive, which is a copolymer composed of 73% tetradecyl acrylate (C14) and 27% octadecyl acrylate (C18). ThermoTape provides strong skin adhesion while reducing skin injury risks and increasing the quality of medical care.

1.4 Current Solutions

1.4.1 High and low adhesion tapes

High adhesion tapes are typically composed of acrylic adhesives and include products such as 3M™'s Durapore™ and Tegaderm™ [3,4]. High-adhesion medical tapes are often used to ensure the protection of wounds from the environment, as well as prevent dislodgement of medical devices with patient movements, especially during sleep. These acrylic high adhesion tapes, such as Tegaderm™ and Durapore™, increase in adhesion over time and need time to fully adhere to the skin. Because the adhesion increases over time, they are used as long-term wear adhesives. Durapore™ is described as a "High-strength Securement Class" surgical tape and is used for securing tubing and catheters and immobilizing fingers and toes. Durapore™ uses a cloth backing that can be ripped from a roll of tape for application. Durapore™ is considered one of the highest adhesion

medical tapes and has been used as a high adhesion benchmark during ThermoTape development [17].

Another high adhesion medical tape, also used as a benchmark during ThermoTape development is Tegaderm™. Tegaderm™ provides a waterproof and sterile barrier, is used for covering wound care dressings, covering and securing IV catheter sites, and securing other devices to the skin, such as nasogastric tubes. It provides a semi-occlusive backing, allowing for wound sites to breath, while protecting the wound from outside bacteria and moisture. This waterproof dressing uses a polyurethane backing that has a high moisture vapor transmission rate (MVTR), allowing for high breathability to facilitate wound healing and limit adhesion reduction from moisture buildup from under the tape from sweat [3]. Tegaderm™ is transparent, allowing for continuous visibility of wound care sites and IV insertion sites. It comes in individually packaged and sterilized dressings, with a liner system that allows for application without touching the adhesive, maintaining sterility. With a polyurethane backing, the tape flexes with the patient's skin, providing comfort and improved wear performance. Tegaderm™ meets the needs for IV-line securement and wound care dressings [18].

A common low adhesion tape KRT, which was described in Section 1.2.2. Low adhesion tapes are often made with silicone adhesives, which offer trauma free release and maintain constant adhesion levels during use, whereas acrylic adhesives increase in adhesive strength over the wear time. KRT comes in rolls which can be ripped off and applied to dressings. As a silicone tape, it does not adhere well to tubing and will often become dislodged [2,13].

We learned about other specific use cases during customer discovery interviews with nurse anesthetists. For IV catheters, arterial lines, and eyelid tape (to prevent corneal abrasion during general anesthesia), 3M™ Transpore™ plastic tape is used. Insertion sites are covered with Tegaderm™. For epidural / continuous nerve block catheters, 3M™ Durapore™ is used. For endotracheal tubes / Laryngeal mask airway tubes, Hy-Tape is used, which is a high adhesion waterproof tape. For central lines (internal jugular, femoral vein, subclavian vein) 3M™ Tegaderm™ dressings are used. Three of the industry standard tapes often discussed in this dissertation are outlined in Table 1.1, with ThermoTape as a reference [2, 3, 4, 17, 18].

Table 1.1: Description of industry standard tapes used as benchmarks in this dissertation.

Tape	Backing	Adhesion Level	Use Cases	Key Features
Tegaderm	Non-woven Polyurethane	High	IV-lines, wound care dressings	Translucent, high moisture vapor transmission rates, conformable, stretchable, long-term wear
Durapore	Woven fabric	Very high	Surgical, securing tubing	Long-term wear, cost-effective, can tear off the roll
KRT	Non-woven fabric	Very low	Patients with at-risk skin, where repeated taping is necessary	Trauma free release, can tear off the roll, can be repositioned

1.4.2 Switchable adhesion tapes

Adhesives having selectable or “switchable' adhesion characteristics are known in the art. Temperature switchable adhesives utilize crystallizable moieties within the adhesive

matrix that provide for temperature sensitive debonding by the application of heat. Representative examples of these types of adhesives are described in U.S. Patents. 5,156,911; 5,387,450; 5,412,035: 8,828,181 and 10,471,681. Schmitt et al. (US 5,412,035) describes a PSA composition containing a crystalline polymeric additive that loses adhesive strength upon heating [19]. The patent discloses a crystalline polymeric additive that is a long side-chain (LSC) crystallizable polymer with a melting point above skin temperature. These existing solutions have industrial uses but are not usable on skin due to their high melting temperatures, which are not suitable for skin use, with ThermoTape providing a safe temperature for skin release [20].

Another product is Appeel Sterile, which is designed to reduce MARSI by reducing adhesion under medical tapes better than off-the-shelf solvents, but is not used in this country, and suffers similar issues as other removal solvents, which includes skin irritation and adhesive residue [21]. Another medical tape product, Comfort Release, is removed with solvents, but the skin adhesion was initially very low and fell off the PI's skin in a few minutes. We measured its adhesion and found low peel force values. Lumina, a company in Sweden, has attempted to address the need of a higher adhesion tape with low-trauma release. Lumina uses an optical wand to reduce tape adhesion before removal. The near ultra-violet light actuated debonding method uses a photo-initiator and that causes a chemical reaction which decreases the cohesiveness of the adhesive [22]. This approach does change the tape adhesion and has been shown to reduce pain upon removal and increase patient satisfaction [23,24]. Cohesive failure can leave adhesive residue on the removal surface, which needs to be removed by a solvent [25]. Additionally, this requires a special radiation device for removal, which must always be available when tape is

removed. On top of increasing costs, the interviewed NSF I-Corps nurses said they did not want a separate device to remove medical tape, and instead preferred heat packs, as these are familiar and are readily available around the hospital.

1.4.3 Solvent wipes

To minimize skin damage and discomfort, medical adhesive removers are often applied to assist in the tape removal process [4]. These include alcohol-based, oil-based, and silicone-based removers [2]. However, these removers have limited functionality since they cannot permeate the tape's backing and must be applied at the adhesive-skin interface while the tape is gently pulled away from the skin. With cloth-backed tapes, these solvents can soak through the adhesive with time, easing the removal process, but lead to irritation and leave significant adhesive residue on the skin. Additionally, neonatal skin guidelines advise against using alcohol and organic solvent-based adhesive removers [2]. Therefore, there is a pressing need for safe and trauma-free adhesive removal.

1.5 Goal

From current reviews of literature and over 150 stakeholder interviews, there is an unmet need for higher adhesion medical tape that can be removed without the risk of MARSI. This dissertation will review the development of ThermoTape, a new high-adhesion medical tape designed for low skin trauma upon release.

Chapter 2: Background

2.1 Pressure Sensitive Adhesives

There are several classes of pressure sensitive adhesives, including hot-melt, emulsion, acrylic, and silicone adhesives. These all have specific use cases, advantages, and disadvantages.

2.1.1 Hot-melt

Hot-melt PSAs are composed of 100% solids, meaning that they do not have a solvent system. They are enabled by tackifiers and oil modifiers, which dilutes the entangled polymer network. Adjusting the tackifier and oil modifier types and ratios allows for tuning properties of the adhesives, such as tack, viscosity, the glass-transition temperature, and the wet-out properties. In addition to tackifiers and oil modifiers, they are composed mostly of thermoplastic resins. This simplifies the manufacturing process, allowing for fast production processes due to the low level of volatile organic compounds. This allows high-speed manufacturing and production line automation, leading to increased overall efficiency. They liquify when they are heated, allowing for coating on a substrate, and cooling leads to hardening and establishment of adhesive strength. This does not require a system of ovens to remove solvents like acrylic adhesives [26]. The disadvantage of hot-melt adhesives is their limited strength. As a thermoplastic, hot-melt adhesives can act as viscous liquids, which means that they are not dimensionally stable under a load. This means that they are mostly used for hold-in-place use cases, and not under load, as they can flow under load over time [27].

2.1.2 Acrylic

Acrylic PSAs are used for high adhesion medical tapes and are lower cost than silicone adhesives. They are formed from crosslinked acrylic polymers. They have relatively high moisture vapor transmission rates, are resistant to heat and humidity, and can be laminated on surfaces. They are also less prone to develop sticky edges, which remain after tape removal, leaving an outline of the bandage. However, as a high adhesion PSA, there is no easy method of removal, which can cause MARSI upon removal. Acrylic PSAs are high adhesion and increase in adhesion over time, and so are often used for long-term wear applications with 7-14 days of wear. The adhesion increases over this period, which further contributes to skin trauma upon removal. Acrylic PSAs are solvent-based PSAs: acrylic polymers in petroleum-based solvents. These PSAs provide improved film formation during manufacturing but are more expensive to manufacture than hot-melt adhesives, which do not have solvents [28]. After coating on a substrate, acrylic PSAs must go through a series of ovens to remove the solvents, which increases complexity and cost. The work presented in this dissertation is enabled by the solvents in the PSA, which dissolve the temperature sensitive additive.

2.1.3 Silicone adhesives

Silicone adhesives have been developed as alternatives to high adhesion tapes, especially acrylic tapes. Silicone adhesives are hypoallergenic and especially biocompatible, so patients with adhesive allergies can usually withstand silicone PSA products. These adhesives can be repeatably applied, are permeable, reasonably water resistant, and have atraumatic removal from skin. However, silicone adhesives are more expensive than acrylic adhesives, they are not strong enough to secure critical medical

devices to skin for mobile patients, and they offer less moisture resistance than acrylic tapes [29].

2.2 Temperature sensitive additives

The problem of developing a temperature sensitive tape for skin use is unique due to the narrow temperature range. The FDA reported in our pre-submission response that 45°C is the temperature limit for heat application on skin. The lower temperature is bound by febrile skin, which can reach 38°C. This gives a range of 38°C to 45°C for a temperature sensitive additive melting temperature for use in ThermoTape. We have identified two classes of TRA materials which melt within this required temperature range. The first class includes long linear chain alkanes and their analogous alcohols. C20 (Eicosane) and C22 (Docosane) alkanes exhibit melting temperatures in the range of 38°C to 43°C, which is within the desired temperature range. Furthermore, these alkanes can be combined into an alloy with a melting temperature that is linearly related to the mole ratio of the two adjacent (e.g., C20-C22) alkanes, allowing the temperature to be tuned for different applications. For example, applying to children may require a lower temperature than applying to adults. Several TRAs were tested in this study, including 1-Tetradecanol, Eicosane, and a custom, long side-chain acrylic polymer that was synthesized in our lab. This crystalline polymeric additive is a copolymer of C14-alkyl acrylate/C18-alkyl acrylate. Different molar ratios were synthesized to achieve a desired melting temperature [30]. The addition of these temperature sensitive additives form a PSA-additive polymer composite.

Chapter 3: Prototype Design, Development, and Lab Testing

3.1 Design

In our development of ThermoTape, we explored the use of a photothermal switch to release adhesion of a temperature-sensitive tape that was developed for non-medical applications [31]. This customized tape system consisted of a near-infrared (NIR) photothermal sensitive tape and a NIR light source device with non-contact thermal feedback control. However, requiring a separate device to remove the adhesive encompasses logistical problems and would increase costs and regulatory challenges.

Thus, we propose the incorporation of temperature-responsive additives (TRAs) as a means of introducing thermal debonding behavior into the adhesive interface, between the PSA and skin or device. These additives can be added directly into the PSA formulation, or they can be selectively applied during manufacturing. For skin contact applications, the thermal debonding temperature must not exceed the skin pain threshold temperature (~45°C) and must be above normal skin temperature (~35°C) and febrile skin temperature (~37-38°C) [32]. We have developed a mechanism whereby the tape is warmed for less than a minute with a heat pack prior to removal, leading to a rapid and dramatic reduction of the force needed to remove the tape from the patient's skin. This novel approach allows for rapid introduction into hospital workflows since heat packs are prevalent in hospital supply systems and are commercially available from multiple sources. This new medical tape system, ThermoTape, requires only a heat pack and is not hindered by having the hospital or clinic stock an additional custom device. Many of

these design decisions were made during the National Science Foundation's (NSF) I-Corps™ program.

3.2 National Science Foundation's I-Corps™

The NSF I-Corps™ is a customer discovery program to evaluate hypotheses teams have about their need and product-market fit. Teams may claim that an unmet need exists, and that they will target it by creating a product with certain features and will launch that product in a specific population with associated commercialization stakeholders. But all those claims remain hypotheses until they are evaluated with stakeholder/customer discovery interviews. Product requirements are created as the result of these interviews. In the design thinking process, the first step is to empathize. This involves discovering people's explicit and implicit needs so that they can be met through your designs. A small development team has a narrow window into what the true need is because they must base it on their experience and literature. This means they may have the need incorrect. This could mean a variety of things, such as the need is not as large as they thought, the need is different than they thought, they misunderstood the need, there are stakeholders who have needs they did not think about or know about, and many other possibilities. Bypassing this emphasize step could result in a team creating a solution that does not address the real needs of their stakeholders and does not have appropriate product-market fit, reducing the odds of success of that potential solution. Stakeholder interviews will highlight the biggest needs that project stakeholders experience. This reveals what the team should focus on addressing with their solution before ideation or prototyping even begins. After these interviews, the team can define the core functions and product

requirements of their potential solution, and then use those as guidelines for ideation, down selection, and finally, prototyping [33]. When I joined ThermoTape, I committed to following this approach, and completed over 150 interviews throughout my PhD. This was done through completing the local NSF I-Corps™ twice, and the national NSF I-Corps™. I will outline our learnings from these programs, which will give context for the design decisions presented in this dissertation.

I started my customer discovery work with ThermoTape in the summer of 2020 with the local NSF I-Corps™. We completed 25 interviews, and spoke with nurses, purchasing managers at hospitals, manufacturers, suppliers and others. The main hypotheses I was testing was learning more about and validating the need, understanding which population had the largest need, and how nurses would like to remove ThermoTape. Our biggest learning was that they did not want a separate device to remove medical tape, and instead preferred heat packs, as these are familiar and are readily available around the hospital. Given this insight, the team moved forward with developing ThermoTape for release with heat packs. We also gained insight into two areas with a large need that ThermoTape could address: IV-line securement and wound care dressings. As both of these markets could be addressed with a similar design, the team moved forward with the goal of one of those markets.

The National I-Corps™ is a 7-week customer discovery program where 100+ interviews are conducted to test hypotheses about the need, market, and product features. I led this rigorous program as the entrepreneurial lead. The goal of our National I-Corps™ in Winter 2022 was to further evaluate our proposed target market of peripheral IV lines (PIVs) with

a direct comparison to the wound care market. We completed 105 interviews during the seven-week period, 27 of which were in person, and 78 were virtual. We had five core questions during this program:

- What kind of tape should we make: sterile or nonsterile, surgical, cloth based, paper based, polyurethane based, adhesion level?
- What use case should we target?
- What population should we target?
- How can we sell to each population?
- What are the stakeholders in the process to commercialize tape?

We had a key moment during the seven-week program. Nurses told us that critical devices kept falling off the patient when the tape fails. We learned that nurses would prefer to have significantly higher skin adhesion to keep critical devices like IV lines and nasogastric tubes secure and maintain wound care dressings to prevent infection, reinjury, and other complications, but that their current high adhesion tapes still lead to regular dislodgement. This exposed an unmet need for higher adhesion medical tape that can be removed without the risk of MARSI. Previously, we thought we could simply match the adhesion level of existing medical tapes and reduce the adhesion upon removal, and that MARSI was the biggest pain point for nurses. Nurses stated consistently that MARSI is not as important to them as device dislodgement. This discovery led to a pivot that has changed our mindset and our requirements. We are no longer tape that just prevents MARSI- the key feature is stronger adherence of critical medical devices. While existing high adhesion tapes have reached the ceiling for adhesion levels as they already cause

MARSI upon removal, we can pass this barrier, as the ThermoTape adhesion level can be mitigated upon removal. We are updating our design to have higher adhesion than current high adhesion tapes to provide higher holding power for critical medical devices on skin, such as IV lines.

I attended the European Wound Management Association & Journées Cicatrisations Conference in Paris during the National NSF I-Corps™. I completed 20 interviews and spoke with wound care physicians, wound care nurses, wound care nurse practitioners, and other stakeholders in wound care. The hypothesis I evaluated was that along with use with PIVs or securing other medical devices to the skin, wound care is one of our top potential markets. This hypothesis was validated: wound care is a top potential market. However, it is not the beachhead market but instead a pipeline market. The need for a higher adhesion tape than existing solutions that could be safely removed was clear. Interviewees indicated that wound care dressings regularly dislodge and that replacing them increases the risk of infection. However, this market is smaller and more complicated. There were numerous wound dressing companies at the event, many with booths and presentations, with products that had unique antimicrobial or biocompatible features. This market is complicated with many competitors when compared to the PIV market. Due to these factors, the team has selected the PIV market as the beachhead. Given the move to PIVs as the beachhead market, polyurethane was chosen as the tape backing, as interviews showed that this is a common backing for this purpose given the breathability and conformability. A specific polyurethane backing was chosen by speaking with manufacturers and suppliers during the I-Corps™ program.

The target beachhead population was selected as children in hospitals. Children have thinner skin than adults and thus are at a greater risk of MARSI [34]. Additionally, interviews indicated that children can be active and “wiggly” in the hospital, and often pick at their tapes as they do not know why it is there, which leads to regular device dislodgement. Our final value proposition was Children’s Hospitals nurse managers will buy high-adhesion medical tape with easy removal so that they can keep their IV-lines and tubes on active, mobile children without causing skin injury upon removal. We decided to focus on IV-line securement as nurses stated that is what is most dislodged in their experiences, in addition to being a simple product. The need in this population was clearly stronger than adults, though the geriatric population was a close second.

Interviews during the National NSF I-Corps™ provided a clear understanding of the stakeholders in the commercialization process for a medical tape and how to sell to each population. This will be discussed in Chapter 7. This work contributed to the journal submission to the Journal of Wound Care: Comparative Single-Blind Clinical Trial with a Temperature-Sensitive High-Adhesion Medical Tape. The I-Corps work contributed to the product definition and trial design. Given the discoveries during this program, we pursued a study design that would demonstrate that ThermoTape had higher adhesion than the standard medical tapes. We interviewed nurses, decision makers at hospitals, coaters, converters, sterilizers, distributors, other medical device founders, surgeons, patients, physical therapists, and adhesive companies, and defined our beachhead market and prototype based on evidence from these customer discovery interviews.

The team is participating in the local NSF I-Corps program in Summer 2023, because customer discovery never stops for a project. We are asking questions such as how a nurse would remove ThermoTape without instruction, how they would use a heat pack to remove ThermoTape, if they use thermal barriers with heat packs, and if they want a visual indicator that ThermoTape requires heat for removal. This recent customer discovery process has led to several important findings. First, we have learned that heat packs in hospitals are typically used for heat therapy, and thus are applied for periods of up to 30 minutes. This is usually done with a thermal barrier. We have learned the typical use cases of various tapes and the use cases for different sizes and types of Tegaderm™. Nurses also indicated that a visual cue would be preferable to indicate that this tape needs to be removed.

There has already been action from these findings, such as a recent pilot study using a thermal barrier with a heat pack during ThermoTape removal. We are looking into methods to provide a visual cue on polyurethane that indicates heat is required for removal. We also have defined the size of the first ThermoTape product. This customer discovery process will continue. As the project matures, new questions will arise, which will need to be answered in customer discovery interviews.

3.3 Material and Methods

In this chapter, the amounts of C20, C22, and C14/C18 in the PSA were varied, and the resulting prototype tape was tested with peel testing and atomic force microscopy (AFM). The PSA wet film drying times and temperatures were also varied and then characterized with peel testing and AFM. The resulting ThermoTape prototype may be

the first practical medical tape that can provide the high adhesion required for secure attachment of medical devices during hospital care, while significantly reducing the risk of MARSI.

3.3.1 Polymer synthesis

All polymers used in this work were prepared using the same copolymerization procedure described in detail in a prior publication [35]. The tetradecyl acrylate (C14) monomer was purified over neutral alumina while octadecyl acrylate (C18) monomer, azobisisobutyronitrile (AIBN) initiator, and toluene were used as received. Initiator and solvent concentrations were held constant at 0.2 and 65 wt%, respectively, while the copolymer composition was controlled by adjusting the molar ratio of C14/C18 monomers. The following will serve as an example synthesis procedure:

AIBN (0.02 g, 0.12 mmol) and C18 (7.82 g, 24.18 mmol) were added to a 50 mL round bottom flask. C14 (2.18 g, 8.12 mmol) and toluene (3.0 g) were added to a separate scintillation vial, homogenized with a vortex mixer, and added to the reaction flask. The vial was rinsed with additional toluene (3.5 g) to ensure complete addition of the C14 monomer. The mixture was allowed to dissolve and sparged with N2 gas for 15 min. The polymerization reaction was performed in a small, heated (85 °C) round bottom flask immersed in a sand bath for 18 h. The mixture was precipitated into ethanol and the copolymer was collected via vacuum filtration. The copolymer was redissolved in a minimal amount of toluene, precipitated once more in fresh ethanol, and dried in a vacuum oven at 60 °C for 24 h to remove trace solvent contamination.

3.3.2 ThermoTape fabrication

ThermoTape is formulated with the temperature responsive additive (TRA) dissolved in an FDA-compliant hybrid acrylic-rubber pressure-sensitive adhesive (AH-115, Henkel). Three different TRAs were tested separately at various wt/wt% mixtures of the TRAs and PSA, with TRAs of the 73%-C18 and 27%-C14 copolymer temperature-sensitive polymer (TSP), 1-Tetradecanol (TET) and Eicosane (EICO). The solid additives of were first added and dissolved in the solvent-based PSA by stirring for 24 hours at room temperature. This solvent borne mixture was subsequently deposited onto a pre-cleaned 50µm thick polyethylene terephthalate (PET) clear backing using a slot die sheet coater (FOM alphaSC, Denmark). This process was performed in a controlled-environment room with the humidity and temperature set at 40% and 70°F, respectively. The resulting coated sheet was then placed into a drying oven for a set time and temperature under varied drying conditions.

3.3.3 Differential scanning calorimetry

Polymer melting points were determined using a TA Discovery DSC 2500 differential scanning calorimeter (DSC). All samples were initially heated to well above their melting temperatures (T_m) at 20 °C/min, cooled below their T_m at 1 °C/min, and reheated at 10 °C/min. All the thermal characteristics reported in this work were taken during the second heating.

3.3.4 Nuclear magnetic resonance

All compositions were verified via NMR using the terminal methyl group for calibration and the secondary side-chain hydrogens as a quantitative comparison.

3.3.5 Peel force testing

Peel testing was conducted with a test apparatus constructed based on Test Method F of ASTM D 3330/D 3330 M [36]. This standard includes different substrates and peel angles. For example, one method includes testing on a stainless-steel substrate with a 90-degree peel angle. The team tested with this method initially, with poor results. Stainless steel has a much larger surface energy than skin. Adhesion relies on a difference in surface energy, so the tape was much higher adhesion on stainless steel than a surface like low density polyethylene (LDPE) [37]. To better match skin's surface energy, LDPE was used for peel testing. Tape is typically removed from skin at a 180-degree angle, so a 180-peel angle was used for peel testing [38].

Adhesive tape was applied to a temperature controlled low-density polyethylene (LDPE) substrate after it reached a target temperature and was left for one minute before initiating the test. The tape was secured to the substrate using a ChemInstruments RD-1000 rolldown machine with a 4.5-pound roller. A standard peel rate of 100 mm/minute was used at a peel angle of 180°. Tape samples were tested at numerous substrate temperatures. The peel force data was analyzed with MATLAB.

3.3.6 Atomic force microscopy

Atomic force microscopy (AFM) was used as scanning electron microscopy did not yield visible results. As a polymeric material, samples had to be sputter coated. This sputter coated layer covered the small surface morphology. As a result, the team moved towards AFM. Surface morphology of the PSA dried coatings was analyzed with AC-mode phase contrast AFM. Images were taken with an Oxford Instruments Asylum Research Jupiter XR AFM using BudgetSensors Tap300Al-G tips. The cantilever was tuned to a free amplitude of 300 mV and operated at a set point optimized to obtain the highest average

phase possible, ensuring the images were obtained in attractive mode at a phase well above 90°.

3.4 Results of manufacturing and lab testing of prototypes

The crystalline copolymer of C14-alkyl acrylate/C18-alkyl acrylate was synthesized with four different molar ratios and tested with DSC alongside pure C14 and C18 (homopolymers) to show the tunability of the melting temperature. Fig. 3.1 shows the melting temperature of the copolymers.

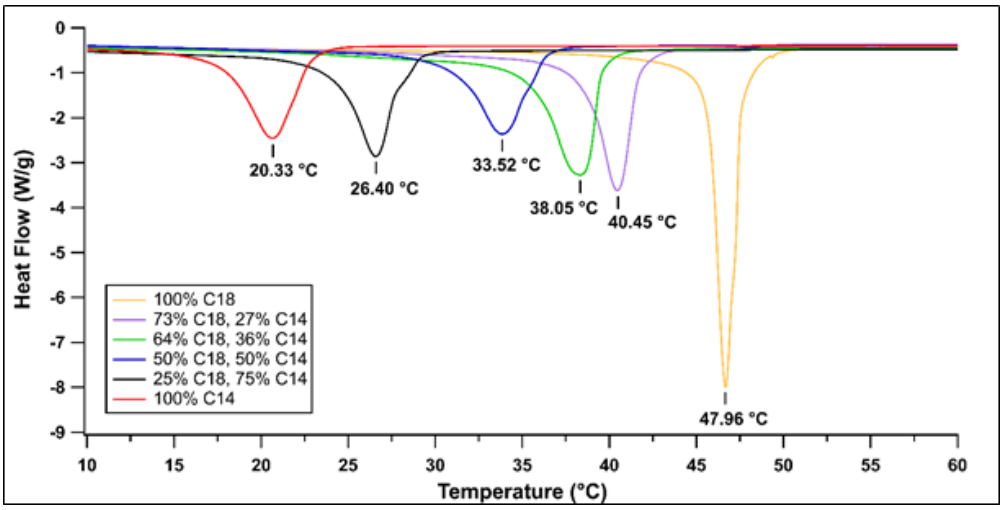


Fig. 3.1. DSC curves for C14 and C18 homopolymers and four C14/C18 copolymers, demonstrating the tunability of the C14/C18 copolymer with varying C14 and C18 molar ratios.

Since the 40.5˚C peak of the 73%-C18 and 27%-C14 copolymer was within the temperature range of interest for adhesive skin removal, this copolymer molar ratio was chosen as the TSP for incorporation into the PSA.

The EICO, TET, and TSP additives were fabricated, and the resultant adhesive was peel tested at 1 and 5 percent (wt/wt%). Fig. 3.2 shows that 1% TSP has the largest reduction in peel strength from 25˚C to 45˚C, at 76% when compared to the other percentages and additives. Next, several percentages around 1% were tested, which is shown in Fig. 3.2b, where 1% TSP again has the largest decrease in peel strength when heated from 25˚C to 45˚C.

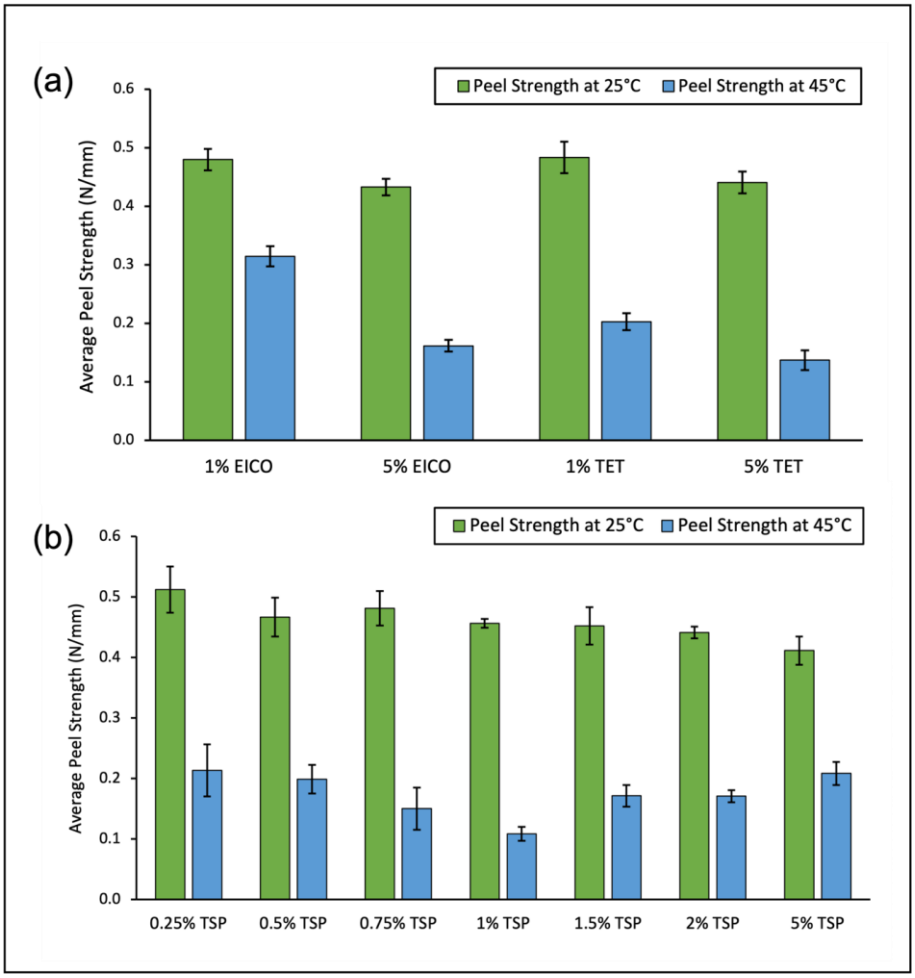


Fig. 3.2. Peel strength data for (a) 1% EICO, 5% EICO, 1% TET, and 5% TET tested at 25˚C and 45˚C, and (b) C14/C18 copolymer TSP percentages at 25˚C and 45˚C.

Several drying temperatures and durations were tested with 1% TSP, with the resultant peel strength data shown in Fig. 3.3. From this data, it is seen that oven drying (solvent evaporation) wet films with 1% TSP at 120°C for 10 minutes has the largest drop in peel strength when heated from 25˚C to 45˚C. This sample was then peel tested from 25˚C to 45˚C in 5˚C increments, and was compared to pure PSA with no additive, and pure C14 and C18 as 1% additives to the PSA, as shown in Fig. 3.4.

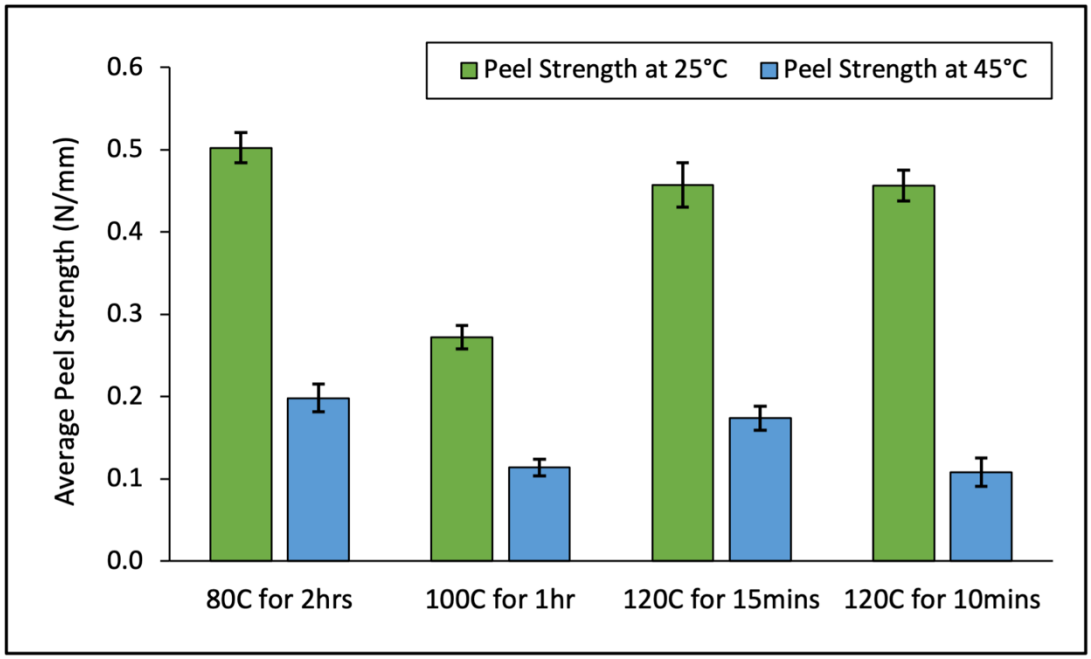


Fig. 3.3. Peel strength data for 1% TSP with varying drying times and temperatures, tested at 25˚C and 45˚C.

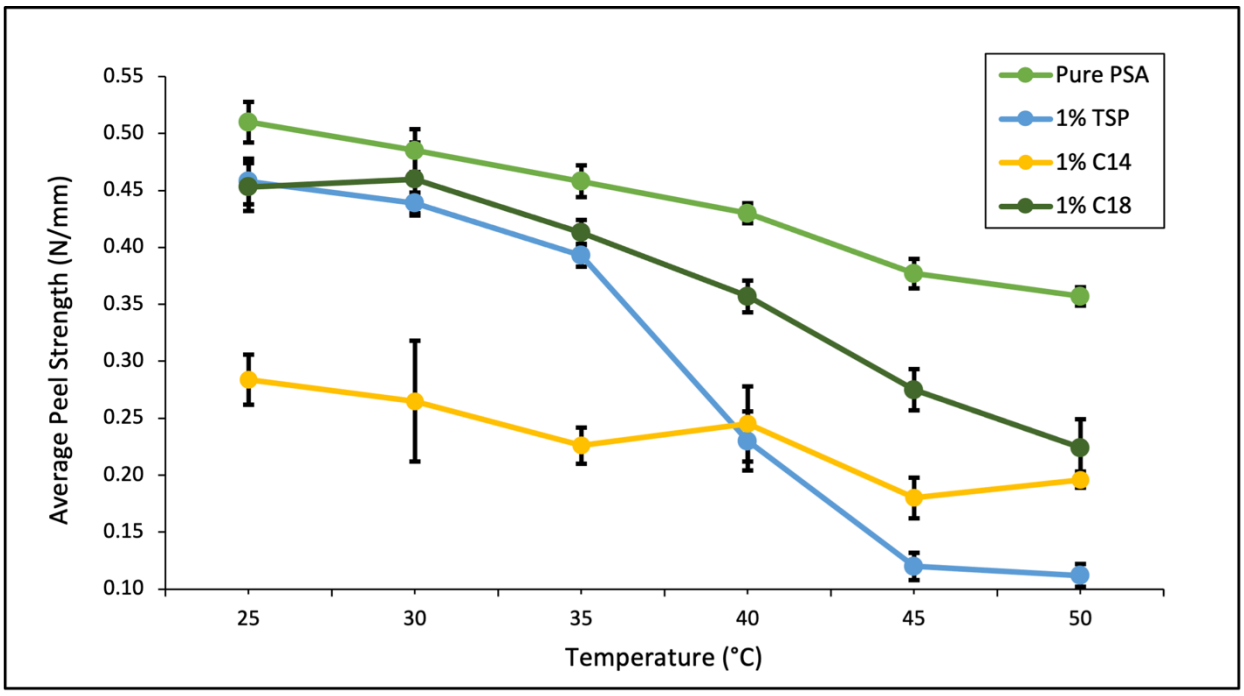


Fig. 3.4. Peel strength curves for pure PSA with no additive, 1% TSP, 1% C14 homopolymer, and 1% C18 homopolymer. Materials were tested at 25˚C-50˚C in 5˚ increments.

In addition to peel testing, all these samples were characterized with AFM. While no TET or EICO samples showed clear surface segregated domains on the PSA exterior (air side), all TSP samples exhibited phase-separated nanometer-sized domains. The formation of these domains appears to be dependent on TSP concentration as well as the drying time and temperature. As shown in Fig. 3.5, the domains increase in size with the increase in additive concentration. Furthermore, Table 3.1 shows that the domains increase in size and overall area when drying time is increased from 10 minutes to two hours, and temperature appears to do the same when increased from 80˚C to 120˚C. The size of these phase separated nanometer-sized domains directly relate to the drop in peel strength with heating, where sizes closer to 30 nm show the largest peel strength drop.

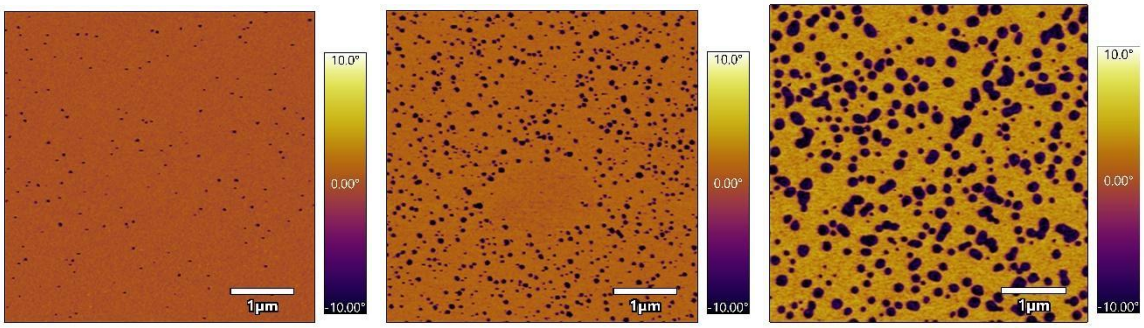


Fig. 3.5. AFM phase images of 0.25% TSP (left), 1% TSP (middle), and 2% TSP (right). Areas of low phase (dark) correspond to TSP nanodomains.

Table 3.1. TSP nanodomains increase in size with the increase in TSP percentage, drying time and drying temperature.

Sample	Average CE Diameter (nm)	Average Area (nm^2)
0.25% TSP 120˚C 10 minutes	8.137 ± 13.45	193 ± 350
1% TSP 120˚C 10 minutes	30. 155 ± 28.389	1350 ± 1820
1% TSP 100˚C 1 hour	78.237 ± 22.882	5220 ± 2930
1% TSP 80˚C 2 hours	77.015 ± 26.918	5230 ± 3410
2.0% TSP 120˚C 10 minutes	130.989 ± 60.985	16400 ± 14700

3.5 Discussion

DSC measurements of TSP confirm that compositions with 27%-C14 and 73%-C18 have the desired melting temperature of 40.45°C, which is in our target range for skin adhesive release. These spectra show that the TSP additive can be predictably tuned for each specific use case, such as synthesizing a lower temperature for neonates and an elevated temperature for young adults in outdoor environments.

The peel strength measurements under temperature-controlled conditions demonstrate that the 1% TSP additive provided optimal performance of high adhesion at the skin temperature of 35°C and significant release at 45 °C, as shown in Fig. 3.4. In comparison to the pure PSA, the addition of 1% TSP retained 89% of the peel force at 35°C. The pure PSA reduced adhesion by 17.7% from 35 to 45°C, and the 1% TSP reduced adhesion by 67.5% from 35 to 45°C. This is due to the combined synergistic temperature response of the PSA and the additive. While neither fully meets the need, the combination of the two materials has a large temperature triggered drop in peel force while retaining a high initial adhesion. Although the relative differences were promising, the 50µm thick PET backing used in these measurements is not representative of a clinically relevant tape for human subjects testing because it is not flexible, and its water vapor transmissive properties are too low.

Atomic Force Microscopy (AFM) phase images of the PSA containing the long-chain alkanes and alcohols (TET and EICO) did not exhibit the phase separated surface domains which were clearly seen in the TSP samples. Furthermore, mixtures of the commercial AH-115 PSA with the alkane additive did not show as strong of a temperature dependent reduction of peel strength compared to the 1% TSP additive made with 27% C14 and 73% C18 as a copolymer, as shown in Fig. 3.2. Based on the AFM images and peel strength measurements, it appears that the long chain alkanes do not phase separate and remain miscible in the PSA following solvent extraction. In the TSP samples, these nanodomains show a different phase than the surrounding PSA material. We assume that these nanodomains are the TSP additive, as the concentration and size of the nanodomains are dependent on the amount of additive, as shown in Table 3.1 and

Fig. 3.5. As the size of the nanodomains grow with a shorter drying time and higher temperature, it is likely that there is still TSP in the bulk of the PSA film upon removal from the oven, and as the film is a given longer time to dry at a lower temperature, the solvent evaporates more slowly, driving more TSP to the surface thereby yielding larger surface nanodomains when drying is complete. With a larger TSP percentage, the domains are larger as there is simply more material, as shown in the AFM images in Fig. 3.5. This demonstrates that the peel strength drop upon application of heat is dependent on the size of the nanodomains. Domains that are too large yield a smaller drop in adhesion upon application of heat, while smaller sizes with sufficient surface area, or concentration, exhibit a larger decrease in peel strength under our test conditions.

During solvent evaporation, nucleation of the crystalline polymer in the bulk PSA takes place. Segregation (TSP nanodomain formation on the PSA surface) is regarded as one of the effective approaches to tune the surface properties of polymer composites because the migration of molecules induces the surface properties different from the bulk, which broaden its applications. It is highly likely that the crystalline polymer has decreasing solubility in the solvent-free PSA and migrates along with the evaporating solvent to the exterior (air side) of the adhesive film. This causes the growth of TSP nanodomains on the PSA exterior surface. The proposed mechanisms for the nanodomain formation process are shown in Fig. 3.6. The growth of these nanodomains is affected by TSP concentration, and the drying duration and temperature.

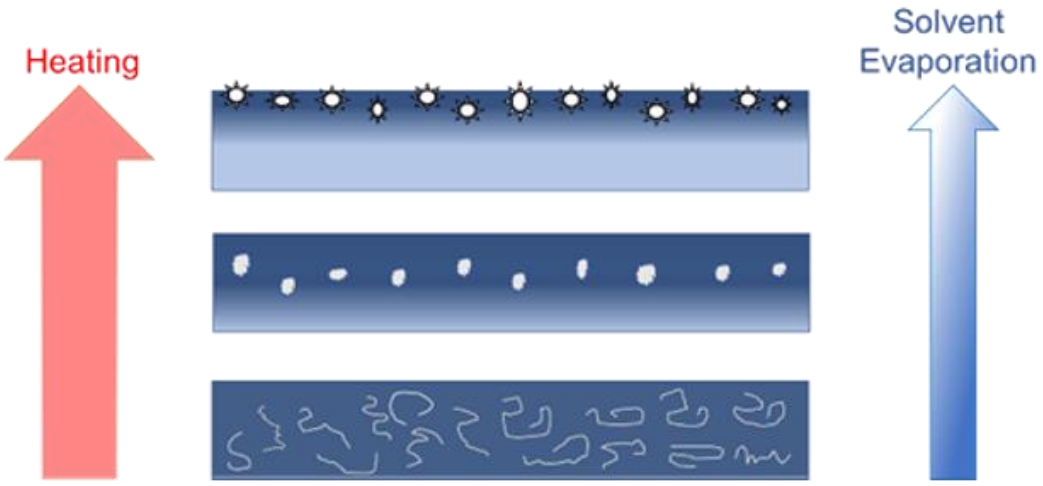


Fig. 3.6. The process of TSP nanodomain formation on the ThermoTape surface. In the bottom, TSP is dissolved in the solvent-borne PSA. As the tape and additive are heated, the solvent evaporates, causing the TSP to begin nucleation and growth. The movement of solvent to the surface carries the growing TSP particles towards the surface. A concentration gradient of the TSP is produced in the PSA along with a significant concentration of surface nanodomains. Upon tape warming, these surface TSP nanodomains melt upon application of heat, forming non-adhesive puddles on the skin-PSA interface. Alternately the melted TSP facilitates PSA cavitation and filament formation during tape removal.

There are two likely mechanisms for the temperature responsive release behavior of the TSP additive. In one scenario upon application of heat, the surface nanodomains melt and coalesce to form “puddles” of non-adhesive material that disrupts the adhesive-adherend interface. These puddles may also act as stress concentrations that will initiate tape detachment upon tape removal. These stress concentrations, or failure points, allow

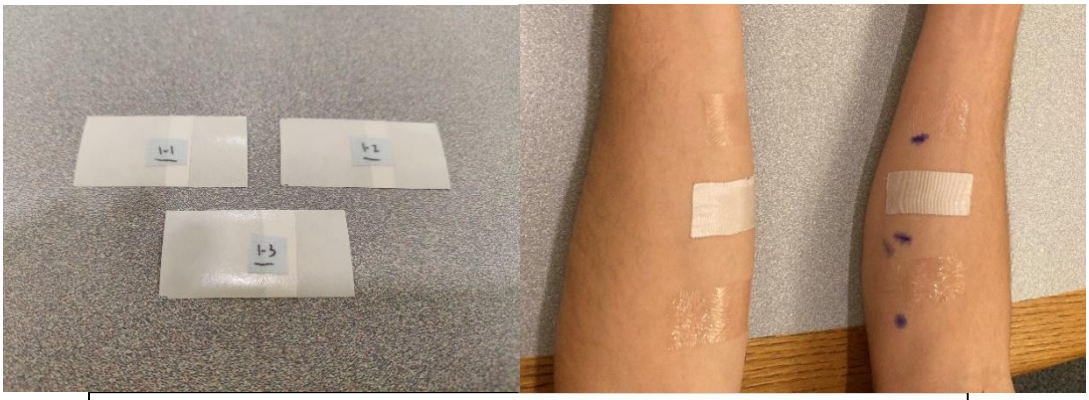
the tape to be removed with less force, acting as nucleation sites for cavity formation during the debonding process. Additionally, TSP is expected to exist as a gradient towards the surface. Alternately, as the surface and near-surface TSP melts, it increases mobility and decreases the resistance to deformation of the PSA, enabling cavity and fibril formation during the deformation and debonding process to occur at a lower force. In either case, the size of the surface domains is a controlling factor in the temperature responsive behavior of the adhesive. We expect that smaller nanodomains can melt quicker and at a lower temperature than the larger ones. While the 0.25% TSP sample did have smaller domains, we expect that the concentration was not high enough to sufficiently disrupt adhesion upon melting. As seen in Fig. 3.4, most of the peel strength drop occurs after 40 °C, where the TSP melts and disrupts adhesion. The temperature dependent peel force curve of the pure PSA shows a modest temperature sensitivity. However, there is an abrupt temperature response for the formulation with 1% TSP close to the melting temperature of the TSP. We envision that C18, which has a melting point of 50°C, mostly follows the pure PSA curve until it nears 50°C. On the other hand, the C14 polymer has a melting point close to 25°C and behaves as an oily surface residue, and so remains at low adhesion levels starting from 25°C. Adding 1% TSP slightly lowers the initial adhesion at 25°C compared to the pure PSA due to the non-adhesive additive on the PSA surface. The 5% TSP additive produced an even larger impact on the initial adhesion. After optimizing a tape system by selecting the base PSA, the optimal temperature sensitive additive, concentration, and drying conditions, there remain several limitations to these study findings.

A limitation in the development of ThermoTape is the method that heat was applied with the peel tester. When heating a tape sample to 25°C from 45°C, it can take the substrate 10 minutes to reach the target temperature, subjecting the tape sample to a 10-minute heat ramp. Once the target temperature is reached, the tape sample undergoes static heating conditions for one minute before the peel test is initiated. Future clinical use will require more rapid warming conditions, where a heat pack is applied to the tape for a short amount of time. Additionally, in vitro testing has a heat source maintained by a PID controller, resulting in a consistent target temperature. However, in vivo testing will apply a heat pack to tape on skin, with blood flow beneath the tape sample acting as a heat sink that will make both heating the tape sample and maintaining the target temperature difficult. The tape in future studies will use a much thinner and more flexible backing material, which should allow more rapid heat transfer. Given these differences between in vitro and in vivo testing, the brand of heat pack used along with the heat pack application time need to be defined with pilot clinical studies. Furthermore, the surface migration of the TSP additive during solvent evaporation is a dynamic process. Dynamic measurements will provide more accurate results which can be used to verify any future analytical models of the migration of the TSP additive during the drying process and TSP melting during heating in vitro. Another limitation is considering the drying temperature and duration. We have demonstrated the relationship of nanodomain growth with TSP concentration, drying temperature and duration. However, the drying temperature and duration used in this study are only suitable for low-volume prototyping in static drying ovens. Large scale manufacturing will use a roll-to-roll (R2R) process at an adhesive coating commercial facility. R2R manufacturing of PSA medical tapes utilizes heated,

forced air solvent evaporation with much shorter drying times. These R2R coaters are multizone, and are cooler in the first zone to remove the low boiling point solvents, and continue in a series of zones that get hotter as they progress, eventually reaching ~120°C. These ovens have significant airflow to further accelerate solvent removal, differing from the static ovens of this study [39]. Given the clear dependance on drying time and temperature of the TSP tape, this poses a unique challenge for ThermoTape to optimize a pilot manufacturing process that consistently yields the desired nanodomain size without compromising R2R speed.

To provide a more representative prototype for human case study testing, a more flexible 4.5µm thick PET backing (PolyK Technologies) was used for testing 1% TSP on skin. Two pilot studies were conducted. In the first study with four volunteers, the coated sheets were cut into 1x3 inch samples, with a two-part liner system to allow for easy application to skin, as shown in Fig. 3.7. Before applying the tape, both forearms were cleaned using isopropyl alcohol wipes and skin markers were used to mark the general locations of the tape, with two inches of spacing between each pair of lines. Following the pre-tape application preparations, 1x3 inch Tegaderm™, Durapore™, and ThermoTape were applied in vertical succession on both arms. After each application, the tape was briefly rubbed in a vertical motion to ensure that the tape fully adhered. Once all the tapes were applied, subjects were given an activity log and requested to not participate in strenuous physical activity for the duration of the 24-hour study. When subjects returned to have the tape removed, they were given a Wong-Baker 1-10 Pain Rating Scale to fill out after each piece of tape was removed. When removing the tape, an edge was lifted and peeled 180º at a consistent rate. If a hair was encountered, the tape was removed following the root

of the hair to the tip. On one forearm, all three samples were removed without heat, and on the other, a Dynarex Instant Hot Pack was used on all three samples. The heat pack was activated and kneaded for one minute before application onto the subject's skin. In a preliminary test, the heat pack was applied to each piece of tape for 10 seconds before being removed. The data in Fig. 3.7 below illustrates that ThermoTape was more painful to remove than Durapore™ and Tegaderm™ without heat. While Durapore™ and Tegaderm™ showed slightly increased pain levels when heated before removal, ThermoTape experienced a 65.6% drop in pain levels. The decrease in pain levels with heat provides initial in vivo validation that ThermoTape can reduce pain upon removal when heat is applied.



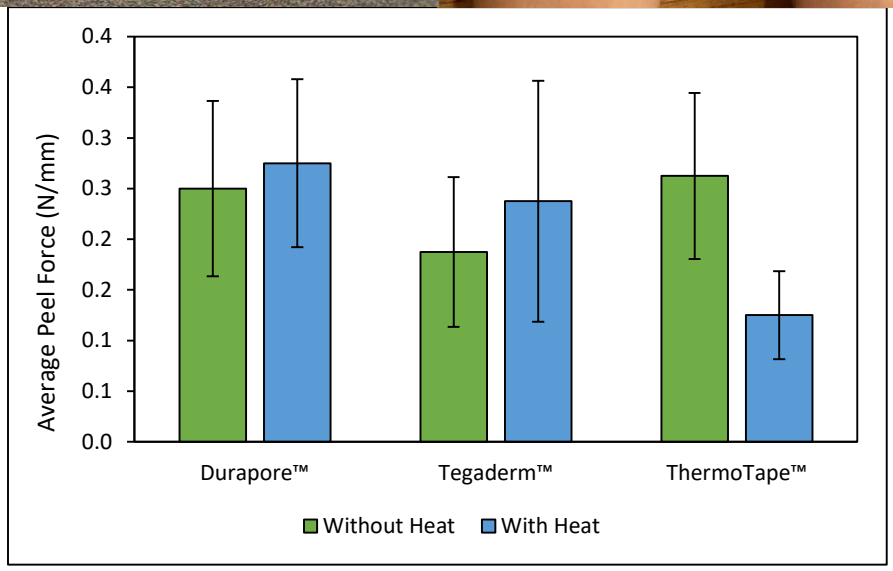


Fig. 3.7: Top left: prepared 1x2 inch 1%TSP ThermoTape prototypes for pilot clinical testing. Top right: 6 samples before removal: Tegaderm™ at the top, Durapore™ in the middle, and ThermoTape at the bottom. Bottom: Pain level data for Durapore™, Tegaderm™, and ThermoTape with and without heat.

The second pilot study had 2 volunteers that had previously exhibited the greatest pain range with tape removal. Given that with in vitro testing the tape is exposed to a heat ramp for 10 minutes, increased heat pack applications times were tested to investigate if pain levels could be further reduced, as ThermoTape removal with heat was still not painless. A previous study (Nielson, et al.) reported that heat application for 60 seconds at 43°C caused long lasting cutaneous hyperaemia, which maintained a 5°C increase in

skin temperature for 15 minutes [20]. With a similar procedure as the first pilot, 5 pieces of 1x2 inch ThermoTape were applied to the forearm. For removal, the heat pack was applied for 0, 10, 20, 30, and 60 seconds. For the first subject, the pain levels progressed as 5, 3, 4, 2, 2, and for the second subject, as 4, 1, 2, 0, 0. This hints that 30 seconds could further reduce pain upon removal when compared to shorter heat application times.

Future clinical trials will use the prototype ThermoTape on the 4.5µm PET backing since full day wearability was easily achievable and estimated vapor transmission is acceptable for experimental human use. Future ThermoTape development and clinical testing in hospital settings will use higher moisture vapor transmission backing materials such as polyurethane and will be tested after sterilization.

ThermoTape is the first temperature-sensitive tape in the human skin temperature range. In vitro testing has demonstrated retention of high adhesion from 1% TSP at normal skin temperature (35°C), and 67.5% reduction in peel force adhesion when raised to 45 °C. Initial in vivo testing has shown a 65.6% reduction in pain when heat is applied prior to removal.

Chapter 4: Clinical Development

4.1 Introduction

The ThermoTape MVP progressed through a series of clinical studies to demonstrate in vivo functionality and refine the prototype. This included a series of pilot tests, a 53-person clinical trial, and another series of pilot tests to prepare for a clinical study at Harborview Medical Center (HMC), a Level 1 trauma and burn hospital for the five state WWAMI region. This approach and the associated results will be presented in this chapter.

4.1.1 Clinical testing of medical adhesives

By basing our protocol on the existing medical adhesive clinical trial literature, we ensured that our protocol aligned with research and industry best practices so that the results yielded useful and publishable data. For the selection criteria, young adults with healthy skin were chosen as the test population to reduce the risk of skin tears. As adult skin becomes thinner and less elastic with age, it becomes more fragile, and thus more susceptible to MARSI [40]. As the first clinical trial, it was important to reduce risk in every possible way by testing on the population with the least risk. Other adhesive studies had a similar age range requirement paired with the exclusion criteria of eczema or adhesive allergies to further reduce risk [41, 42]. To eliminate a possible variable, tape location was randomized in our studies. Wear may be higher in one location when compared to another location. This systematic bias is eliminated by randomizing tape application locations. Other trials generated randomized locations for medical adhesive placement with a computer program [41, 43, 44]. In initial clinical testing, the intent was to demonstrate that the activation of temperature sensitivity reduced adhesion. While future clinical tests did

not limit moisture exposure, early studies limited moisture exposure to allow for focusing on the temperature sensitive mechanism instead of the ability to resist moisture. In other published studies in the literature, subjects were asked to avoid getting the adhesives wet to best test the adhesion of the tapes on skin [41,42]. Tapes had been applied on the volar forearms with locations marked off for consistency in another referenced study [43]. Tapes were rubbed with the applicant's finger following application to the subject's skin to ensure that they would adhere consistently, such as in other studies [41, 43]. Tape removal was performed similarly in another trial, where a corner was lifted, and then the tape was removed at a 180° angle [43]. Tegaderm™ and KRT were selected as product benchmarks products for our study, as both tapes were used in previous studies and represent commercial standards of higher and lower adhesion tapes, respectively [45, 46].

4.1.1.1 Pain, wear, and redness scales and measurements

Pain, wear, and redness are often measured in adhesive clinical research. Many other studies focused on tape wear, pain self-reported from removal, and erythema (redness), and were also assessed in our studies following the measurement procedures from these previous studies [41-44, 47]. The pain scale is used for the subject to self-report their perceived pain during the removal process and is reported immediately after removal. This is used to quantify the pain experience during medical tape removal. There are several types of pain scales used in adhesive clinical studies. In some previous studies, the visual analogue scale (VAS) was used to measure pain, and it was found that there is a 0.94 correlation factor between VAS and other pain scales, allowing the pain scale to be a preferential pick, so the best scale can be used for each study and correlated with

each other [42,43]. The Wong-Baker/faces pain scale is recommended for cross-cultural interactions when compared to VAS, so Wong-Baker was selected for use in our studies [48]. The wear scale is used to quantify how much wear a medical tape experienced over a time period. This scale quantifies how well the tape maintained adherence to the skin during the performance period and is usually correlated with the strength of skin adhesion. Higher adhesion tapes will demonstrate less wear, as they are more strongly adhered to the skin. Wear also is affected by the moisture vapor transmission rate, which is discussed in 4.1.1.2. Quantifying wear allows for estimates of how well medical tapes will perform in clinical settings. The redness scale is used to characterize MARSI. MARSI is defined as skin redness that stays for 30 minutes after removal, and redness can indicate damage to the skin during removal. The wear and redness tables and Wong-Baker images that are used are from a clinical study by Krejsa, et al [49].

4.1.1.2 Moisture vapor transmission rates

The moisture vapor transmission rate (MVTR) measures the ability of a medical tape system to allow moisture to pass through, or in simpler terms, the breathability of the system. Medical tape backings have variable MVTRs and are an important design feature. PSAs also have a MVTR, which depends on the thickness of the film. The MVTR of the PSA is often the rate limiting material when selecting the MVTR of a future medical tape [50]. Woven backings have high MVTRs, but are opaque, as are several non-woven backings. Non-woven polyurethane offers high MVTRs and are transparent, which are features that are critical for wound care applications, such as covering IV lines. High MVTR is a key feature for wound care tapes, as a high MVTR enables oxygen and moisture transport to the wound, which can facilitate wound healing [57]. A high MVTR

can also assist with long-term wear capabilities. A higher MVTR will prevent moisture buildup under the adhesive, as it can pass through the tape [51]. Table 4.1 below shows various backings and adhesives with thicknesses and MVTR values, which were defined through ASTM E96 testing.

Table 4.1: MVTR values of different tapes and backings

Backing or product	Thickness	MVTR (g/m2-day)
PET [53.3]	4.5um	152
PET [53.3]	50um	13.7
LOCTITE DURO-TAK AH 115 PSA coated polyurethane) [51.2]	30µm (PSA)	97
LOCTITE DURO-TAK AH 115 PSA coated polyurethane) [51.2]	50µm (PSA)	60
ArgoMedPLUS® 18411 Polyurethane film [51.1]	25µm	1000
ThermoTape [51.2, 51.3]	50µm AH-115 PSA coated on 50µm PET	13.7
ThermoTape [51.2, 51.3]	50µm AH-115 PSA coated on 4.5µm PET	60
ThermoTape [51.2, 51.3]	50µm AH-115 PSA coated on 25µm polyurethane	60
Tegaderm™ [51.4]	47µm: PSA and polyurethane backing	278

The PET MVTR values were estimated with the well-established film thickness MVTR scaling law (1/t) and PET film data from Mitsubishi [52, 53]. Given the MVTR of a Mitsubishi untreated 12µm PET film is 57 g/m^2/day, the MVTR for our 4.5µm PET backing will be approximately 2.67 times greater (12/4.5) than the 12µm Mitsubishi PET material, yielding an MVTR of around 152 g/m^2/day. The 50µm PET used for in vitro testing has an estimated MVTR of 13.7, significantly lower than the 4.5µm PET. The 25µm

ArgoMedPLUS® 18411 polyurethane film has a much higher MVTR of 1000 g/m^2/day [54].

While the differences in these three films are high, these films are coated with a PSA, which typically has a lower MVTR than the backing film does. As such, in many cases the PSA will be the limiting factor that determines the MVTR of the coated film. Henkel reports that the MVTR of the AH-115 PSA used in ThermoTape is 87 g/m^2/day, when a 30µm film is coated on polyurethane [55]. The MVTR of the polyurethane film that the PSA is coated on is likely well above 87 g/m^2/day, and so we can conclude that this value pertains to the MVTR 30µm PSA film. Scaled up to a 50µm thick film of PSA, we get an MVTR of approximately 60 g/m^2/day. With this data, we can hypothesize that the MVTR of the 50µm PET ThermoTape with a 50µm thick PSA coating is 13.7 g/m^2/day, limited by the MVTR of the film. In the case of the 4.5µm PET film, we can hypothesize that the MVTR of 4.5µm PET ThermoTape with a 50µm thick PSA coating is approximately 60 g/m^2/day. This MVTR value would be the same if ThermoTape was coated on the much higher MVTR 25µm ArgoMedPLUS® 18411 polyurethane film, as the 50µm PSA film will be the MVTR limiter. These values are smaller than the estimated MVTR of Tegaderm™, which is 278 g/m^2/day [56].

As discussed in Section 4.1.1.4, MVTR is not the only determinant of long-term wear. A patent filed by Henkel Adhesives showed that a minimum MVTR is required, and higher numbers will not necessarily add to the long-term wearability [57]. MVTR cannot be used to predict wear, as other variables contribute to long-term wearability. Other aspects that contribute to the long-term wear of a medical tape relate to the backing and the adhesive. For the backing, the other major contributors are conformability and stretchability, which

are discussed in Section 4.1.1.4 below. In this patent, Henkel describes a PSA formulation based on AH-115 that includes two other significant chemical components: plasticizer and tackifier, with the plasticizer improving the PSA flexibility and conformability. The patent application implies that these additives provide extended wear times. Table 4.2 from the patent shows various MVTR values associated with their wear time determined from a clinical study. The MVTR value of a 30µm film of AH-115 (patches C and D) was under 100 (g/m ^ 2)/day. If only MVTR was considered, such an adhesive would be expected to produce a low wear adhesive; however, Patch D provided a wear time of at least 18 days. The UV hot melt acrylic adhesives had very high MVTR values of around 850 (g/m ^ 2)/day (Patches A and B) and had lower wear times, despite their high MVTR values. The solvent acrylic polymer-based adhesive had a MVTR value of less than 400 (g/m ^ 2)/day and was applied onto polyurethane nonwoven backing. This also had a wear time of at least 18 days. While MVTR is an important factor for long-term wear, once a sufficient value is reached, PSA chemistry plays an important role. From Table 4.2, 97 appears to be a sufficient MVTR to achieve long-term wear if other backing features like stretchability and confirmability are met. While a 50µm film of AH-115 has a lower MVTR (60 (g/m ^ 2)/day) than the 30µm AH-115 film in Table 4.1 as it is thicker, Henkel has indicated that AH-115 is an adhesive engineered for long-term wearability at a variety of PSA thicknesses, so this different in MVTR should not be an issue. This assumption was tested in long-term wear pilot studies in this chapter.

Table 4.2: MVTR values and wear times for various medical tapes

Patch	Adhesive (polymer)	Facestock	MVTR (g/m^2)/day	Wear Time (days)
A	UV hot melt acrylic	PET non-woven	857	7 to 10
B	UV hot melt acrylic	PET non-woven	841	1 to 2
C	Acrylic rubber hybrid (LOCTITE DURO-TAK AH 115)	PET non-woven	97	12 to 13
D	Acrylic rubber hybrid (LOCTITE DURO-TAK AH 115)	PU non-woven	97	18 to 20
E	Solvent acrylic	PET non-woven	372	14
F	Solvent acrylic	PU non-woven	372	18 to 20
G	Rubber (styrene-block co-polymer) hot melt	PU Film	194	less than 1
H	Rubber (hydrogenated styrene-block copolymer) hot melt	PU Film	12	1

This table also displays the ranges of wear times for medical adhesives. Some adhesives are meant to be changed daily, or every other day, such as patches H and B in Table 4.2. These are short-term wear adhesives, with an industry example of KRT. Some adhesives are engineered to stay on skin for over 7 days, such as patches C-F in Table 4.2. These are long-term wear adhesives, with an industry example of Tegaderm™.

4.1.1.3 Seasonal considerations

The large clinical trial in this chapter was completed in summer during a heat wave. If this trial was completed in winter, there would likely be slightly different results. While there could be more wear from heavier clothes worn in winter, sweat can be more significant in intense heat. Despite high MVTRs of existing tapes such as Tegaderm™ and Durapore™ (Table 4.1 above), sweat buildup in intense heat is difficult for even the highest MVTR tape to deal with. Sweat will disrupt the skin – adhesive interface and can lead to easier tape removal. For a clinical study, this means that pain values will be lower than they would be in winter, where there is little sweat buildup [58]. This may be partially countered

by having subjects enter the room and acclimatize for 30 minutes to give the sweat buildup a chance to dissipate through the breathable backing and PSA system.

4.1.1.4 Medical adhesive backings

Medical adhesive backings are chosen for their specific application. During initial development for in vitro testing and verification, thick PET films are used due to their ease of fabrication with small scale fabrication methods. A thick PET film, around 50µm, lays flat during slot die coating and is easy to handle compared to thinner backings during transfer steps to the coater and the ovens. This enables simpler characterization for profilometry, as creases are limited and it acts like a flat surface, enabling consistent profilometry measurements and thus consistent data. It also allows for simple peel testing, as a thicker backing will not stretch during a peel force test. As peel force is measured in newtons/millimeter, a backing that stretches during peel testing will yield inaccurate data, as a stretchable backing will add to the millimeters in the measurement. Furthermore, PET is solvent and temperature resistant, allowing for coating of solvent borne PSAs directly on the PET film, as well as drying at high temperatures. However, once a project transitions to industry, thicker PET films cannot be used for medical tapes because they lack several key properties that are important for long-term wear. There are several important factors to consider when selecting a medical adhesive backing for clinical use. These include conformability, lay flat capability, the MVTR, and stretchability. This means that the backing needs to be compliant, breathable, and thin [59]. These characteristics are not associated with thick PET backings, which have a low MVTR, and do not stretch or lay flat on the skin. We used 50µm thick PET for our earliest stage pilot testing in Chapter 3. While we were able gain initial verification of temperature sensitivity, the

thicker backing would not stay on the skin for long periods due to the low MVTR, and the lack of lay flat properties and stretchability. A high MVTR will allow for moisture to be transmitted quickly, while a low MVTR will result in moisture buildup between the adhesive and the skin, disrupting the skin adhesive interface, and thus reducing adhesion, leading to increased tape wear and eventual dislodgement. A backing lacking lay flat properties will have edges and corners that do not flat against the skin. These edges and corners are initiation points for wear, decreasing the performance of the tape and leading to premature tape dislodgement. Additionally, a lack of lay flat properties is typically associated with a lack of conformability to the skin. A thin backing that lays flat will conform to the crevasses of the skin, resulting in stronger adhesion to the skin, including the edges and corners, reducing wear.

Stretchability is another essential characteristic for wear performance and comfort for the patient. As a surface, skin moves in all directions and stretches with body movement. If the adhesive backing is unable to move with the skin, it will resist the natural movement of the skin. This puts stress on the skin-adhesive interface, decreasing wear performance and comfort. For example, polyurethane backings on tapes like Tegaderm™ can stretch in all directions, woven fabric backings on tapes like Durapore™ can stretch diagonally, and PET films cannot stretch. A stretchable backing or one that can move with the skin increases comfort and wear performance [60,61].

Another important backing feature is transparency. Depending on the use case, a backing may need to be transparent. This allows the caretaker to see the securement of the medical device, the IV line, or the wound care dressing [62].

Backings can be woven or non-woven. Woven backings are used in tapes in Durapore™ and look like woven cloth. They are created by weaving yarns together. When stresses are applied transversely to a woven backing, much like cloth, the backing can move with the skin. Woven backings allow for tape removal with the assistance of a solvent, as the solvent can soak through the woven backing. Non-woven backings are made with natural or synthetic fibers, which have been interlocked thermally, chemically, or mechanically. Polyurethane is an example of a non-woven backing. Tape with these backings cannot be removed by soaking a solvent through the backing. Instead, the application of solvent must be applied only in the exposed narrow crease while the tape is being removed causing an extended duration of pain and resulting skin trauma [51,62]. In our case, clear non-woven backings are our broadest use case, whereas woven backings are not transparent, which limits their use cases.

Polyurethane semi-occlusive backings are more expensive but have high MVTRs while also being transparent, allowing for IV attachment and wound care applications. In these cases, a wound is present, making a high MVTR even more important, as this high oxygen and moisture transport can facilitate wound healing [63]. Polyurethane is stretchable and has excellent lay flat properties, making it a common backing for long-term wear adhesives. Polyurethane is not solvent or heat resistant, complicating the manufacturing process, discussed in Chapter 6.

Clinical testing in this dissertation has been completed with 4.5µm PET. As this is ultrathin, it has a reasonable MVTR of around 60 (g/m ^ 2)/day (Table 4.1) and lay flat properties, allowing for use for clinical testing, even for up to a week. From Table 4.1, the same PSA was coated as a 30µm film on polyurethane and achieved 18 days of wear.

The solvent and heat resistant properties of PET allow for coating and drying directly on the backing. Ultrathin PET would not be used clinically due to the higher cost and lower long-term performance compared to polyurethane due to the lack of stretchability, but the ease of fabrication in a lab setting makes it an attractive backing for pre-roll-to-roll manufacturing clinical testing.

4.1.1.5 Types of studies

There are two most common adhesive clinical studies: single blind clinical trials and randomized controlled clinical trials (RCT). A single blind clinical trial is easy to run, only requiring the subject to be unaware of what each tape is and how that tape should perform. RCT is more difficult and is the gold standard of medical adhesive testing. An RCT involves having subjects randomly assigned to two groups, with one group receiving the intervention, and the other receiving the control. To qualify for an RCT, there are checklists that must be submitted with the associated publication that verify that the RCT conditions were met [64]. For the purpose of pre-roll-to-roll manufacturing testing, a single blind trial is standard. RCTs are for more advanced products shortly before or after product launch. A RCT may be pursued later in the development process.

4.1.1.6 Repetitive applications vs. one-time applications

Adhesive clinical trials typically test single medical adhesive application and removal. However, to mimic some medical situations, some clinical trials test repetitive medical tape application and removal at the same site [65]. Clinically, there are many situations that require medical adhesive application and removal at the same site repeatedly. This can occur with patients with chronic illnesses who require regular medical care with similar procedures at the same location, or patients with cancer who have implantable

ports [66]. Repeat adhesive application and removal results in compounding skin damage over time, making these patients more susceptible to MARSI. Each removal can weaken or remove a thin layer of the dermis, damaging the skin and making it thinner in that area [67]. While these studies are more difficult to run, they are a useful tool to test the ability of an adhesive to prevent MARSI, as this is a difficult scenario to maintain healthy skin. This study will be pursued in future ThermoTape trials with sterile, manufactured, and packaged samples.

4.1.2 Heat packs

Heat packs are used for various heat therapies to increase blood flow to facilitate healing and relieve pain. Tension in muscles and soft tissue can constrain blood circulation, which sends pain signals to the brain. Heat packs application dilates blood vessels, increasing blood flow, which also increases oxygen and nutrient transport to the injured area, potentially facilitating the healing process. This superficial application of heat also stimulates thermoreceptors in skin and deeper tissues, which can also reduce pain [68]. Heat packs or pads are also used to warm patients in the case their body temperatures drop. This can occur when patients get an IV, blood transfusion, or just finish surgery [69].

There are several different types of heat packs, which include onetime use, reusable, and electric. Electric pads are used at home, hospitals, and by physical therapists, and can maintain a specific temperature, with mechanisms to prevent overheating. Both one-time use and reusable heat packs must have sufficient heat capacity. High specific-heat capacity materials are used so that they gradually release heat over time. Reusable and one time use heat packs are typically chemical based, except for microwavable heat packs. Microwavable heat packs usually contain natural materials that can absorb heat

from the microwaves. Reusable heat packs are commonly made of a supersaturated solution of sodium acetate in water. They are activated by flexing a notched metal disc, which releases a small amount of sodium acetate crystals that were adhered to the disc. Once released in the supersaturated solution, these sodium acetate crystals function as nucleation sites for sodium acetate crystallization. This triggers immediate crystallization as a rapid exothermic reaction. These heat packs can be re-used by boiling them, which dissolves the sodium acetate crystals, allowing the process to be repeated and the heat pack reused [70].

One time use heat packs are often based on magnesium sulfate. When the heat pack is activated, anhydrous magnesium sulfate contacts water and releases heat in a non-reversible exothermic reaction. The amount of magnesium sulfate and water determine the change in temperature (delta-T) as a result of the exothermic MgSO4/water reaction. The net temperature change of the heat pack depends on the initial temperature of the heat pack plus delta-T. Medline and Dynarex heat packs use this chemistry. One time use heat packs also often use sodium thiosulfate and water solutions with a similar approach to the magnesium sulfate heat packs [71].

Heat packs are commonly used in hospitals and disposable, single use heat packs are recommended to reduce the risk of infection. The current clinical practice is to activate the heat pack and place it on the patient for a long period of time. Heat packs are used for therapeutic purposes, and thus are applied for longer periods of time, usually up to 30 minutes. Given the long period of application, thermal barriers, like a paper towel, are used between the skin and the heat pack [71, 72].

4.2 Additional materials and methods

4.2.1 Tape fabrication

1 *wt/wt%* 73%-C18 and 27%-C14 copolymer temperature-sensitive polymer (TSP) was dissolved in the solvent-based LOCTITE DURO-TAK AH 115 PSA (Henkel Corporation, Dusseldorf, Germany) by stirring for two hours at room temperature while 4.5µm thick polyethylene terephthalate (PET) substrate sheets were prepared. Each sheet was fixed by its corners and side-centers to a sheet of paper which maintained PET rigidity during fabrication and handling. The substrate-liner sets were cleaned and sanitized with a quick spray of general use quality electronics duster and then with a five-minute cycle from a model 256 ultraviolet-ozone (UVO) cleaner (Jetlight, Irving, California, USA). They were then pneumatically fixed to the stage of a slot die sheet coater (FOM Technologies, FOM alphaSC, Copenhagen, Denmark) inside a controlled environment room that was set to 21℃ and 40% humidity. The coating program was set to dispense 600µl/min and travel the bed at 6cm/min. A 30ml syringe was filled with the PSA-TSP mixture and loaded into a syringe pump. The slot die was primed with the mixture, positioned to one end of the PET sheet, and lowered to allow clearance for a 0.203mm feeler gauge between the meniscus guide plate and the substrate. The mixture was dispensed to allow meniscus formation with a length of about 3cm or less. When the film deposition was complete the die head was raised, and the film-PET-paper composite was removed from the pneumatic stage and put into a nitrogen cure oven (VWR International, Randor, Pennsylvania, USA) at 120℃ for ten minutes. This process was repeated until the mixture was exhausted. Each cured composite was covered with a sheet of Slick Paper silicon release liner (Oil Slick, Bellingham, Washington, USA) and rolled once with a 4.5kg roller to ensure uniform

application. The uncoated and nonconforming areas were trimmed with a commercial grade paper cutter and a set of final cuts provided our desired 2.54 x 5.08 ± 0.24 cm (1.00 x 2.00 ± 0.09 inch) geometry.

4.2.2 Tape characterization

AFM and peel testing were performed on a sample from each sheet of ThermoTape to ensure that each sheet would perform as expected in the trial to verify the presence of nanodomains. Peel testing was performed on a 1X3cm sample from each coated sheet of ThermoTape to ensure that each sheet would perform as expected in the trial. Highest quality ThermoTape was verified to have a 70% drop in peel force from 25 to 45°C.

4.2.3 Tape preparation

Prior to application, ThermoTape and Tegaderm™ Transparent Dressing Film (10.1 cm X 10 meters, 3M™, Saint Paul, Minnesota, USA) were prepared in 2.5 cm X 5.1 cm samples. ThermoTape was prepared with a liner system that allowed for a similar application style as Tegaderm™, where the adhesive is not touched during application. 2.5 cm X 5.1 cm of KRT (2.5 cm x 5 m, 3M™, Saint Paul, Minnesota, USA) was peeled from the roll and cut at the time of tape application.

4.2.4 Study design and setting

The study has a clinicaltrials.gov Identifier of NCT05449600 [73]. This was a single blind clinical trial; therefore, the subject was unaware of the tape identities, and that warming would decrease adhesion in one of them. To minimize the risk to the subjects, the inclusion and exclusion criteria were selected to reduce the risk of skin tears during the

trial. The inclusion criteria specified subjects 18 to 25 years old. The exclusion criteria included a history of eczema, MARSI, or allergies to medical adhesives.

Flyers advertising the study (Appendix A.1) were posted around the University of Washington Seattle campus with a link to an application form (Appendix A.2). The survey collected their gender and emails and verified that the subjects were 18-25 and did not meet any of the exclusion criteria. If they were eligible for the study, they could then use a scheduler (Appendix A.3) to select a time slot for tape application and removal. When the subjects arrived at their appointment, they were given a written consent form (Appendix A.4) to read and sign before tape application. Tape application and removal took place in a temperature-controlled building.

Before tape application, both undersides of the forearms were cleaned using a 70% isopropyl alcohol prep pad (Clever Health, Mansfield, Massachusetts, USA), with one wipe used per arm. A surgical skin marker (Viscot Medical, East Hanover, New Jersey, USA) was used to draw lines to indicate the areas of tape application. The first area of tape application was 3.8cm distal to the elbow, with the second and third areas 5 and 10cm distal to the first area, respectively. Following the pre-tape application preparations, ThermoTape, KRT and Tegaderm™, were applied to each forearm in a location specified by a spreadsheet. This spreadsheet was output by a Python program, which provided random placement locations for the three tapes on individual forearms for all 53 subjects. A single researcher applied and removed all tapes from the subjects to eliminate inter-operator variability. The tapes were applied with the 5.1 cm length wrapping around the forearm. After each application, a finger was used to rub the tape on the forearm to ensure that the entire tape area was fully adhered. Once all tapes were applied, subjects were

requested to not participate in strenuous physical activity and to not get the tapes wet for the duration of the 24-hour study. The limitation on strenuous physical activity was implemented to reduce sweat. The team wanted to limit moisture buildup under the tape and focus on demonstrating the outcome of pain reduction with applied heat. This moisture buildup could have reduced the peel force upon removal or led to increased tape wear. Future trials will allow a wide range of physical activity. Subjects were given an activity log to record any physical activity (Appendix A.5). The log included details on the activity, duration, and the state of the tape after the activity.

When subjects returned to have the tapes removed, the team went over the activity log and ensured that they did not get the tape wet or participate in strenuous physical activity. Each piece of tape was analyzed for wear before removal using a 0-7 scale, as shown in Table 1. A visual pain scale of 0-10 was placed in front of them, and the removal process began. After each piece was removed, the subject would be asked to report their pain on a 0-10 scale, as shown in Fig. 2. Tapes were removed from the right arm first without the use of a heat pack. Removal was initiated at an already lifted corner, or if all corners were adhered, a corner was lifted, and the tape was peeled at 180° at a constant rate. The peel rate depended on the strength of the adhesion. If adhesion was high, the tape was peeled slower to avoid skin tears. If adhesion was low, the peel rate was faster. If a hair was encountered, the tape was removed following the root of the hair to the tip.

Tape on the subject's left arm was removed with the same procedure as above, but a Dynarex Instant Hot Pack of dimensions 5'' by 9'' (Dynarex Corporation, Orangeburg, New York, USA) was applied to each tape prior to removal. Prior to heat pack activation, the corner of each tape sample was lifted so that removal could begin right after heat

pack application. The heat pack was then activated and kneaded for one minute before application and applied to the tape for 30 seconds before removal. Each piece of tape was removed immediately after warming. The heat pack was kneaded for 20 seconds between each tape removal and then applied to the next tape, and the process was repeated.

Each subject was asked to wait 15 minutes following tape removal to examine for skin redness caused by removal. As demonstrated by Krejsa, et al, there is little change in redness between tape removal and 30 minutes' post removal, so a shorter time was used [49]. After 15 minutes, the redness from the removal site was visually inspected in comparison with surrounding skin and recorded on a 0-4 scale. The reduction in redness was found by calculating the percent change in the recorded redness for tape removed with and without heat. Subjects were emailed a $50 Tango Card® after completing the study.

In the case that a skin tear occurred, Vinyl gloves and Brava Adhesive Remover Wipes (Coloplast, Minneapolis, Minnesota, USA) were available to aid in tape removal. Neosporin (Johnson and Johnson Consumer, Skillman, New Jersey, USA), and First Aid Sheer Adhesive Pads (7.6 cm X 10.2 cm, Rite Aid, Camp Hill, Pennsylvania, USA) were available to treat the tear.

4.2.5 Statistical analysis

Statistical analysis was performed in Excel, with two-tailed paired t-tests and binomial distribution functions used to show statistical significance. Results were considered significant when $p \leq 0.05$.

4.2.6 Ethical considerations

This study was approved by the University of Washington IRB committee B. This trial has been registered with ClinicalTrials.gov (NCT05449600). All subjects were given written informed consent before tape application. The inclusion and exclusion criteria lowered the risk of skin tears, and the researchers were prepared with Brava™, Neosporin™, and bandages in the case tape removal was not possible without inflicting skin tears or high levels of pain. Subjects were informed to indicate if pain was too high, in which case Brava would be used to assist with removal.

4.2.7 Heat pack test design

A variety of heat packs were tested to understand their heating profiles and suitability for ThermoTape removal. The most popular one-time use heat packs used in hospitals, as well as three reusable heat packs (not typically used in hospitals), were evaluated. Medline Infant Heel Warmer, Medline Accu-Therm Hot Pack, Medline Instant Hot Pack, Cardinal Health Instant Hot Pack, Dynarex Instant Hot Pack, Med Pride Instant Hot Pack, HotSnapZ, Snappy Heat, and HTG Hot to Go were tested. Heat packs were tested with the Total-Range Traceable Thermometer, 4015CC. One heat pack was tested for each datapoint. Each heat pack was tested with several different methods. To measure the temperature of the heat pack itself, the heat pack was activated and folded around the thermometer, and the temperature was recorded at 10 second intervals. It is also important to measure the heat pack temperature against skin, as blood flow can act as a heat sink. In another method, after activation, the heat pack was placed against the skin on the underside of the forearm of a study subject, with the thermocouple between the skin and the heat pack, and the temperature recorded at 10 second intervals. The transition to skin was further characterized by activating the heat packs, waiting until they

reach their maximum temperature, and then applying it to the skin, with the thermocouple between the heat pack and the skin, to characterize the temperature drop when applied to skin.

4.3 Results

4.3.1 Heat pack results

The reusable heat packs reached high temperatures, as expected. The maximum temperature as stated by the manufacturers of these heat packs were 54.4°C for HotSnapZ, 54.4C for Snappy Heat, and 54C for HTG.

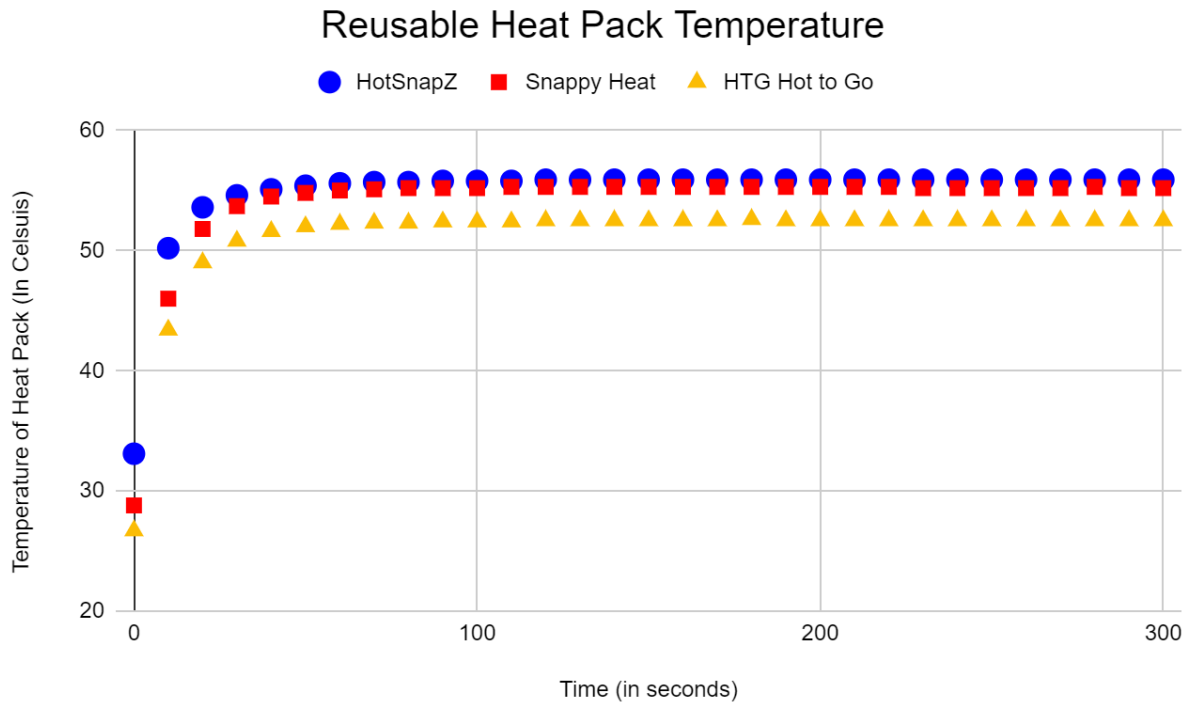


Fig. 4.1: HotSnapZ, Snappy Heat, and HTG heat packs tested for 300 seconds after activation.

As seen in Fig. 4.1, the measured temperatures were close to the reported temperatures. All three of these reusable hot packs are quick to heat up and maintain a steady temperature over time. These were also tested on skin, with the data shown in Fig. 4.2.

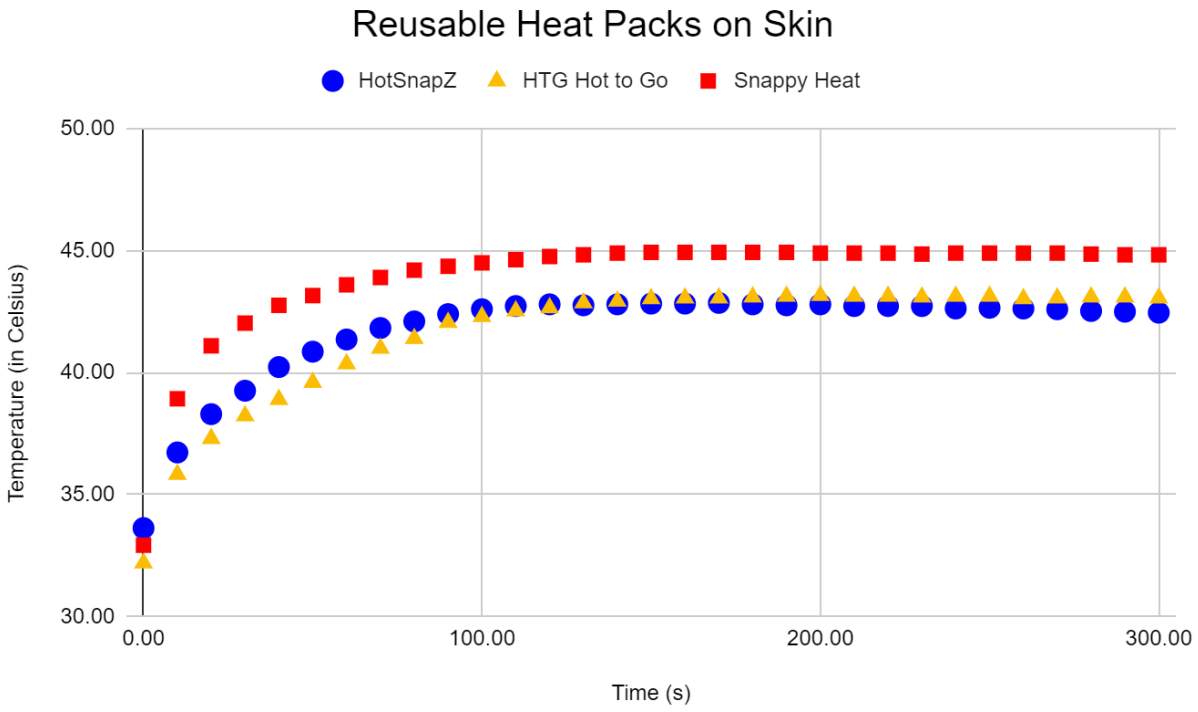


Fig 4.2: HotSnapZ, Snappy Heat, and HTG heat packs tested for 300 seconds after activation on skin.

The temperature for the reusable heat packs drops significantly- nearly 10ºC, when placed on skin. The temperature rises much slower on skin compared to the data in Fig. 4.1, taking nearly 100 seconds to reach its maximum temperature.

The single-use heat packs vary in their temperature range. A few of these heat packs report their maximum temperature, with the Medline Infant Heel Warmer at 40.6°C, and the Dynarex and Med Pride instant hot packs at 50°C. Fig. 4.3 shows the single-use heat

pack temperatures over time. Dynarex, Med Pride, and Medline's Instant Hot Pack are the hottest hot packs and exceed the target temperature of 43°C, with Cardinal Health at 43°C. Medline's Accu-Therm and Infant Heel Warmer are below 40°C.

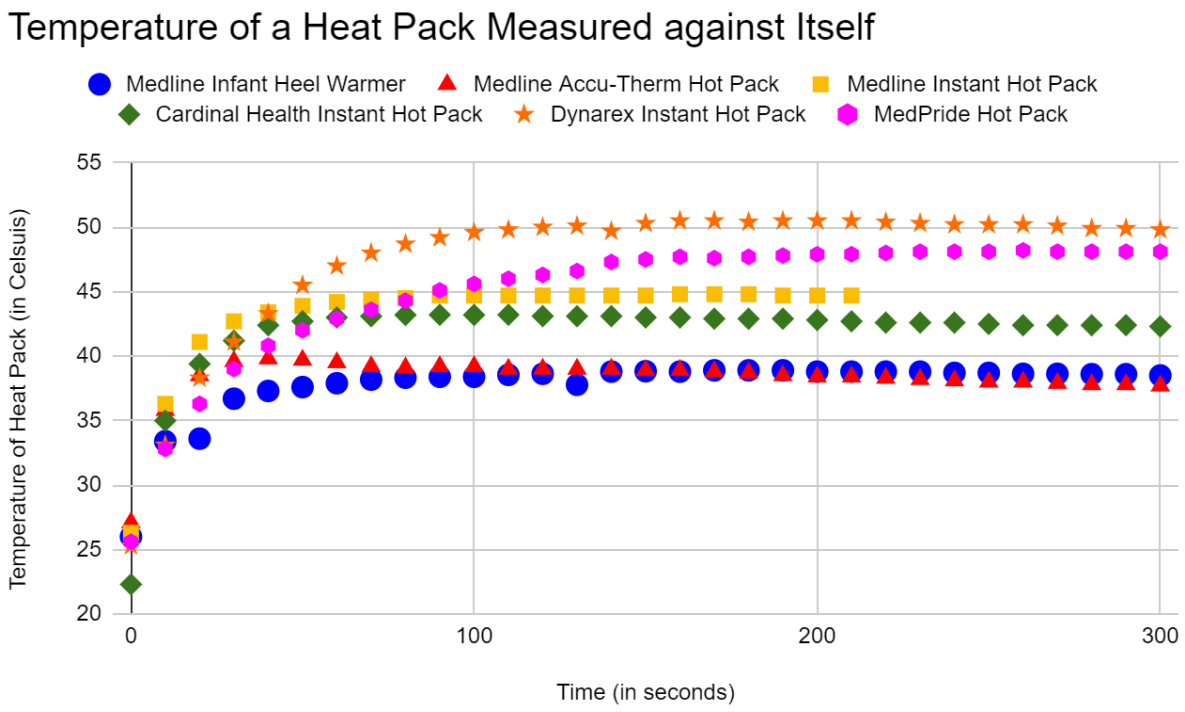


Fig. 4.3: Single-use heat pack tested for 300 seconds after activation.

These heat packs were applied to skin, with the data shown in Fig. 4.4. On bare skin, Med Pride's heat pack reaches the highest temperature at 41.3ºC, around 230 seconds after activation. Dynarex's heat pack has the next highest temperature at 39.7ºC at 170 seconds. Cardinal Health's hot pack is third, with a maximum temperature of 37.2ºC also at 170 seconds. Medline's Accu-Therm is fourth, with a maximum temperature of 36.1ºC reached at 40 seconds. Last is Medline's Infant Heel Warmer with a maximum temperature of 35.7ºC achieved at 120 seconds.

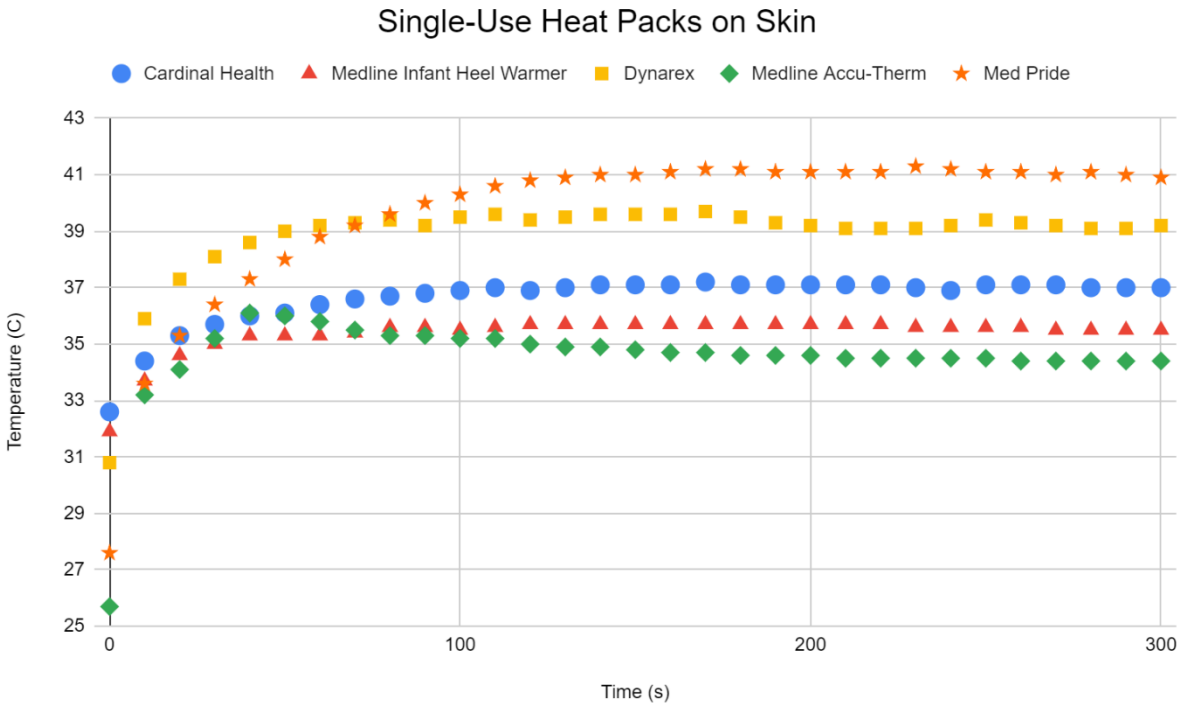


Fig 4.4: Single-use heat pack tested for 300 seconds after activation on skin

To further characterize the drop in temperature when applied to skin, the heat pack was activated and placed onto the skin when it reached its maximum temperature. The maximum temperature was based on data from Fig 4.1 and 4.3. Fig. 4.5 below shows the data for the temperature drops of the different heat packs when applied to skin. Medline's Infant Heel Warmer exhibited a temperature drop of 1°C when applied to skin. Cardinal Health had a temperature drop of 1.2°C. Dynarex had the largest drop in temperature with a decrease of 3.4°C. Medline's AccuTherm the lowest drop in temperature when applied at 0.9ºC. Med Pride had a decrease of 1.3ºC, comparable to Medline's Infant Heel Warmer and Cardinal Health's heat pack.

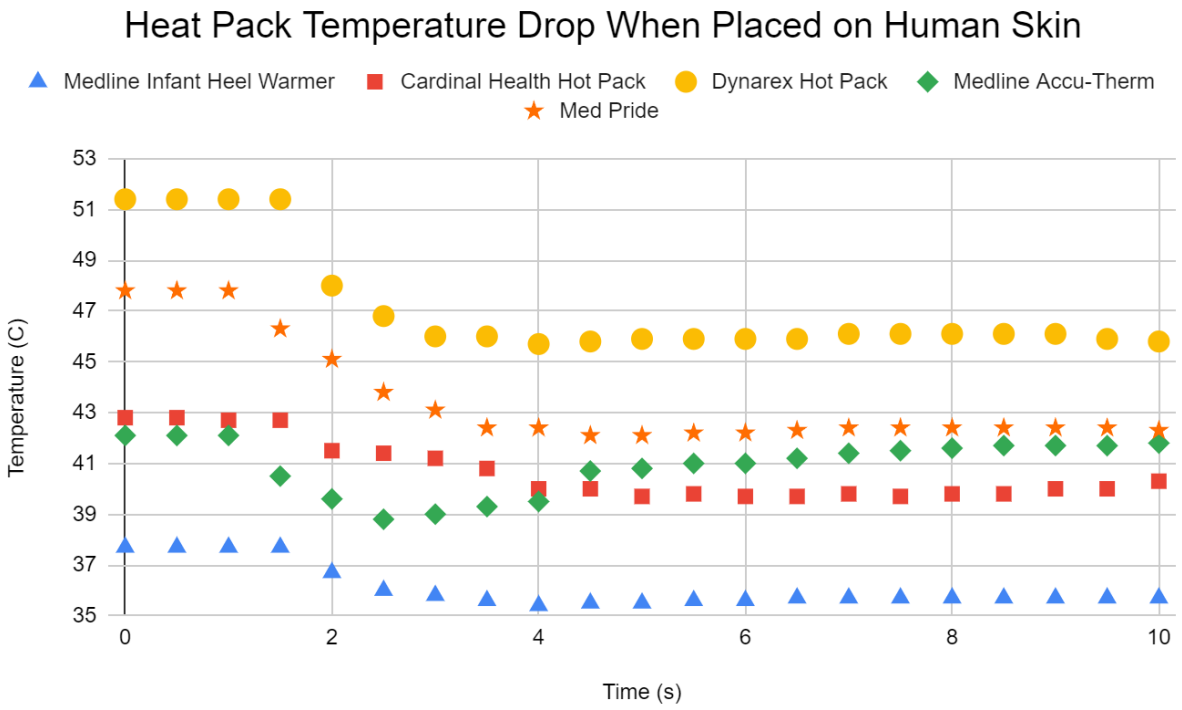


Fig 4.5: Heat pack temperature drop when placed on human skin.

4.3.2 Clinical trial results

Previous pilot tests showed a 66% reduction in pain was observed in human pilot clinical testing [20]. This follow-on study is a clinical trial to compare ThermoTape performance against industry standard high and low adhesion medical tapes.

The primary outcomes from this trial include quantifiable data on tape wear, pain during removal, and skin redness after removal. 131 potential subjects completed the clinical trial subject application, as shown in Appendix A.3. 19.1% of these respondents reported allergies to adhesives, and 13% reported a history of eczema, which led to 95 eligible subjects. Subjects reported seeing flyers in the libraries and hearing about the study via word of mouth. 54 subjects had tape applied, and 53 subjects returned for tape removal.

One subject did not return for removal. Of the 53 that completed the trial, the results from 7 subjects were removed for the following reasons. Two subjects went swimming. One had slight irritation around several tapes when she returned for removal and admitted that she had a history of mild eczema but did not report it on the survey. For one subject, the heat pack was too hot on her skin, and so a paper barrier was applied. To be consistent with all other subjects, this subject was removed. An additional 3 subjects had some tape that completely fell off. For the analysis, these subjects were removed as there are no associated pain or redness values. This gives a total of 47 subjects with complete data for comparative analysis.

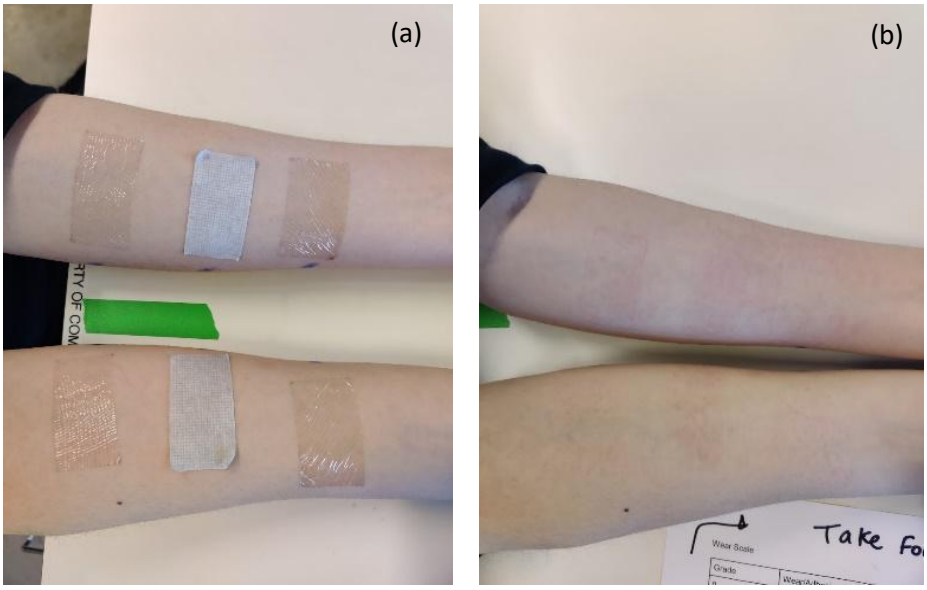
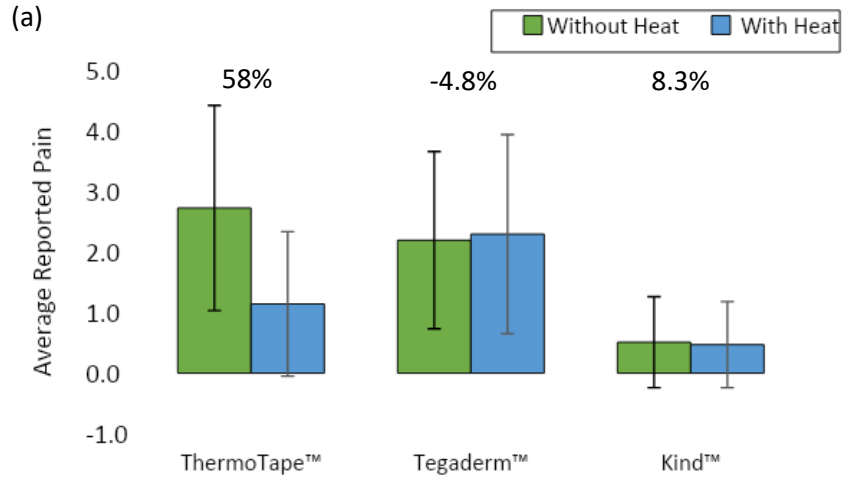


Fig. 4.6: Subject forearms (**a**) 24 hours after application and right before removal, with ThermoTape, KRT, and Tegaderm™ randomly placed on the left and right forearms and (**b**) 15 minutes after removal to document the redness.

Fig. 4.7: The Wong-Baker 0-10 pain measurement scale that was used in this clinical trial.



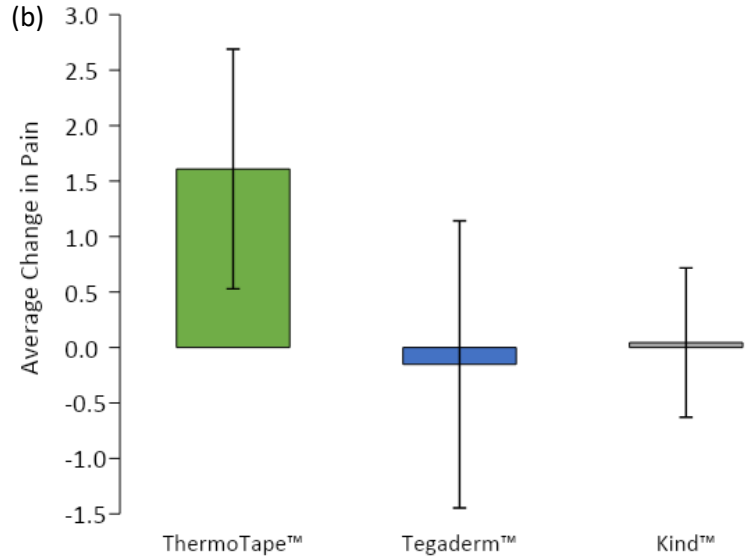


Fig. 4.8: (**a**) The average reported pain with and without heat, with the percent change in pain before and after heating reported on the chart, with 58% for ThermoTape, -4.8% for Tegaderm™, and 8.3% for KRT and (**b**) the associated average change in pain when heat was applied.

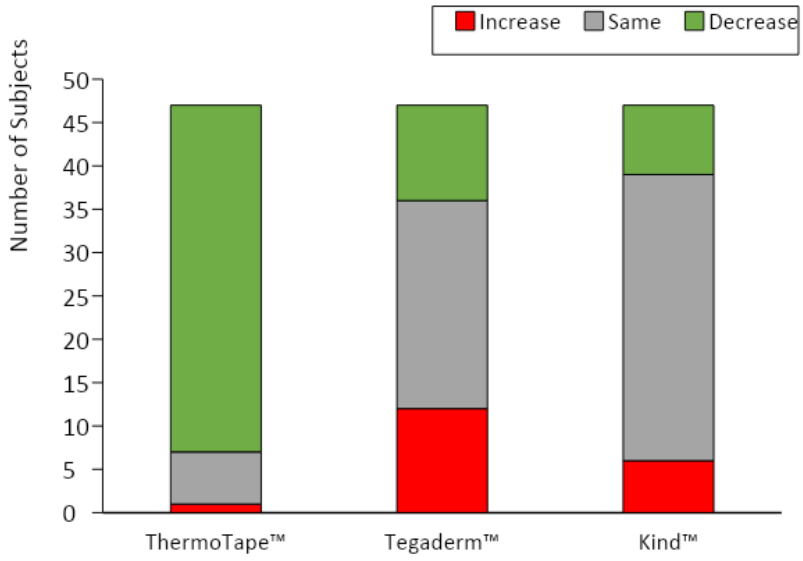


Fig. 4.9: Sign test for the difference in pain before and after heat. An Increase indicates that pain increased with heat, Same indicates there was no change in pain with heat, and a Decrease indicates that pain decreased with heat.

As shown in Fig. 4.8, the percent change in pain before and after heating is 58% for ThermoTape, -4.8% for Tegaderm™, and 8.3% for KRT. A paired t-test for ThermoTape with and without heat yields a p-value of 3.74E-13, 0.43 for Tegaderm™, and 0.66 for KRT. A sign test shows the difference in pain before and after heating. An Increase indicates that pain increased with heat, Same indicates there was no change in pain with heat, and a Decrease indicates that pain decreased with heat. Fig. 4.9 shows that most subjects for ThermoTape experienced a decrease in pain with heat, with just one subject

having an increase in pain with heat. Out of 47 subjects, 40 saw a decrease in pain with heat, and 36 of those 40 saw a decrease of 50% or more. Of the 6 that saw no change in pain, 4 of these subjects had pain values of 0 with and without heat, so there was no possibility of a decrease. Tegaderm™ and KRT showed most subjects did not have a change in pain with heat, with a similar number showing an increase or decrease. A binomial distribution function was used on the number of Increase and Decrease values, with the Same values left out. This yielded a p-value of 1.91E-11 for ThermoTape, 0.66 for Tegaderm™, and 0.39 for KRT. Fig. 4.8 shows the average difference in pain by subtracting the pain score with heat from the pain score without heat. The average difference in pain for ThermoTape is 1.57, with a paired t-test p-value of 6.11E-13. Tegaderm™ and KRT have average differences in pain close to zero, with paired t-test p-values of 0.58 and 0.66, respectively. Comparing the clinically relevant conditions of Tegaderm™ with no heat and ThermoTape with heat, the average pain difference is 1.05, with ThermoTape having a lower average pain. The paired t-test p-value of these two datasets is 3.6E-8. ThermoTape without heat and Tegaderm™ without heat have an average pain difference of 0.53, with ThermoTape having a higher average pain.

Table 4.3: The wear scale used in the clinical trial

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

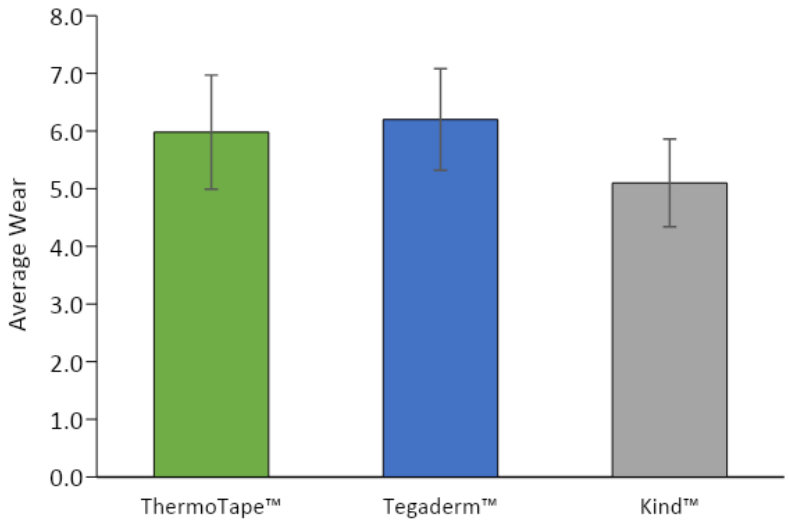


Fig. 4.10: Average wear values 24 hours after application for ThermoTape, Tegaderm™, and KRT. The left and right forearms were combined, so this data consists of 94 samples of each tape.

Wear values for both arms were combined into Fig. 4.10 above. ThermoTape exhibited slightly more wear than Tegaderm™, with a paired t-test p-value of 0.054. ThermoTape and Tegaderm™ exhibited less wear than KRT, with paired t-test p-values of 5.35E-11 and 1.02E-18, respectively.

Table 4.4: The redness scale used in this trial

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

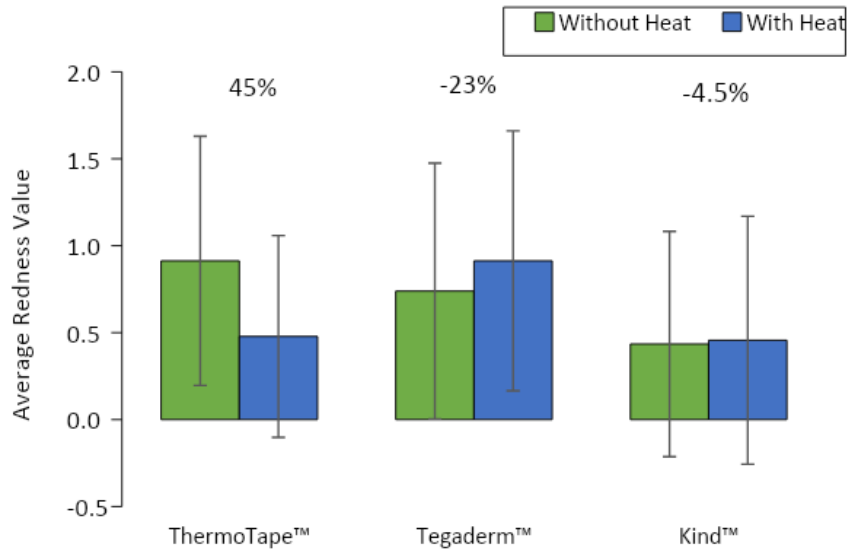


Fig. 4.11: The average redness from tape removal with and without heat, with the percent change in redness with and without heat reported on the chart, with 45% for ThermoTape, -23% for Tegaderm™, and -4.5% for KRT

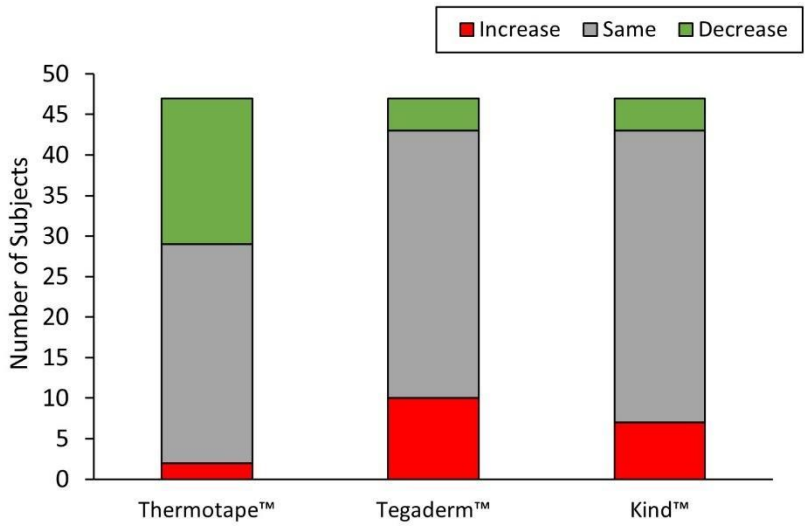


Fig. 4.12: Sign test for the difference in redness before and after heat for ThermoTape, Tegaderm™, and KRT. An increase Indicates that redness increased with heat, Same

indicates there was no change in redness with heat, and a Decrease indicates that redness decreased with heat.

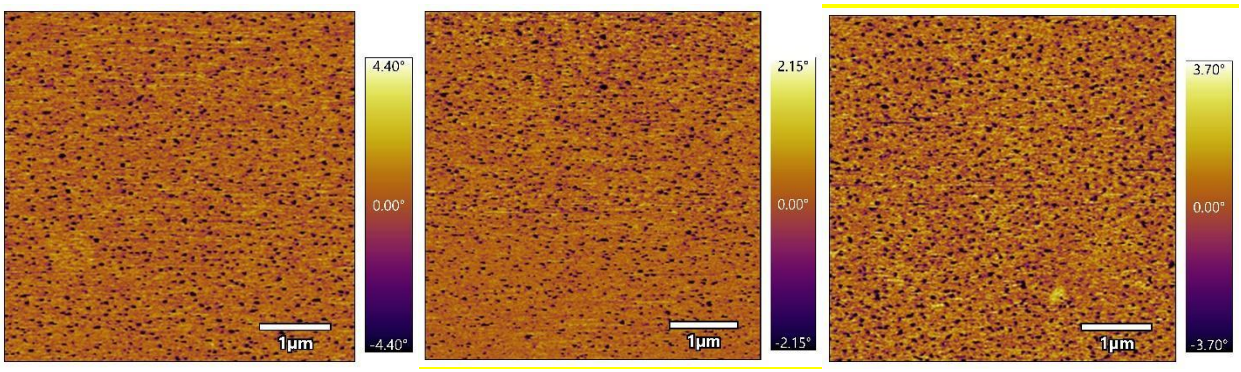


Fig. 4.13: AFM phase images of ThermoTape samples used in the trial. Each of these images are from a separate sheet. Areas of low phase (dark) correspond to TSP nanodomains.

As shown in Fig. 4.11, ThermoTape had a 45% reduction in redness when heat was applied before removal, with an associated paired t-test p-value of 1.8E-4. Tegaderm™ had a 23% increase in redness when heat was applied prior to removal, with an associated p-value of 0.07. KRT had a 4.5% increase in redness when heat was applied before removal, with an associated p-value of 0.8. As shown from the sign test in Fig. 4.12, 18 subjects saw a decrease in redness with heat with ThermoTape, while 2 saw an increase in redness with heat. Of the 27 who saw no change in redness, 15 were zeros with and without heat. Most subjects did not experience a change in redness for Tegaderm™ and KRT with and without heat. A binomial distribution function was used on the number of increase and decrease values, with the same left out. This yielded a p-value of 4.02E-4 for ThermoTape, 0.18 for Tegaderm™, and 0.55 for KRT.

Our lean process controls, analysis feedback loops, and growing familiarity with the process allowed an increase in quality that was visible from the meniscus area reduction of the fabricated sheets and consistent AFM images as seen in our prior publication [20]. AFM testing of all 26 sheets from 4 batches yielded an average circle equivalent (CE) diameter of 48.72nm, with a standard deviation of 13.04nm. AFM phase images from three sheets are shown in Fig. 4.13. Peel testing from each batch verified that all batches used in the trial exhibited at least a 67% reduction in peel strength from 35°C to 45°C. The average peel strength reduction of the batches used in the trial was 72% with a standard deviation of 4.8%.

4.4 Discussion

4.4.1 Heat pack discussion

The reusable heat pack data showed that all three heat packs reach over 50ºC and get to that temperature quickly, but when applied to skin, this temperature drops 5-10ºC and the heat packs take longer to reach their maximum temperature. However, the temperatures are above 43C, and so are suitable for ThermoTape application. These heat packs are not used in hospital systems, but they remain an option for consumer and non-hospital use. Given the high temperature of these heat packs, they would likely need to be used with a paper towel as a thermal barrier.

Data from Fig. 4.5 of the heat packs on skin shows that Med Pride's heat pack reaches the highest temperature, but it takes the longest the longest to reach that temperature. Dynarex's heat pack has a lower maximum temperature than Med Pride, but it achieves it in a shorter amount of time. Dynarex hits maximum temperature before 100 seconds, which would be useful for skin application, where application times are short. All of these

heat packs, like the reusable ones, experience a large drop in temperature when placed on skin. Generally, it was observed that heat packs that exhibit a higher temperature before application to the skin have a higher decrease in temperature when applied. Comparing the temperatures of Fig. 4.4 and Fig. 4.5 indicates that allowing the heat pack to reach its maximum temperature, and then applying it to the skin, leads to a much higher temperature for the heat pack on skin. In the case that a heat pack is not warm enough for ThermoTape removal, waiting 2-3 minutes and then applying it will result in a higher heat pack temperature when applied to the skin. Fig. 4.3 shows that Dynarex has the highest temperature when compared to the other 5 single use heat packs. While Fig. 4.4 shows that when applied to skin, the MedPride heat pack has a higher temperature, the MedPride heat pack takes longer to reach this temperature than the Dynarex heat pack. Given the desired short heat pack application time in the clinical setting, a heat pack that quickly heats up on skin is needed. The Dynarex heat pack provides this feature, as well as high temperatures, and so was selected as the heat pack for clinical testing. The Dynarex heat pack is applied to skin 60 seconds after activation. Fig. 4.3 shows that after 60 seconds, Dynarex will be nearing its maximum temperature, increasing the temperature of the heat pack when it is applied to skin. The Medline Infant Heel Warmer was tested as it is the only heat pack that is used on neonatal patients. Given the thin skin of neonates, hotter heat packs cannot be used. Adhesive removal is a big issue for neonatal care, as their skin is fragile, and solvents cannot always be used to assist removal, as solvents can damage their developing skin. As a result, MARSI is especially prevalent in neonatal intensive care [74]. ThermoTape would be a great solution for these neonates with this heel warmer heat pack. However, given the low temperatures of this

heat pack, this population will require a TSP with a lower transition temperature, which can be a future product.

4.4.2 Clinical trial discussion

The inclusion and exclusion criteria were chosen so that subjects had a minimal risk of skin tears during the trial. Given these precautions, no skin tears occurred during the trial. The trial provided statistically significant results supporting pain reduction of ThermoTape with warming. The minimum clinically significant difference in acute pain was defined in a prior study, with a threshold around 12 out of 100 for the visual analogue scale for the general population, and 10 for children aged 8-15 [75, 76]. Modifying this for our similar 0-10 scale given the 0.94 correlation factor between the two scales, this would be around a 1.2 difference for the general population or 1 for children for clinical significance. Additionally, since the change in pain of 1.57 was above 1.2 on the 0-10 pain scale, this result is deemed clinically significant. This means that the patient can feel the difference between ThermoTape with and without heat. This is paired with statistically insignificant results supporting pain reduction for Tegaderm™ and KRT with warming. As a single blind study, the subject was unaware of the tape identities, and that warming would decrease adhesion in one of them. Additionally, tape location was randomized on each arm- so ThermoTape and Tegaderm™ may have been in the same forearm location for some subjects. As seen in Fig. 4.6, ThermoTape and Tegaderm™ were indistinguishable from each other on skin, further reducing bias. This is further supported by the statistically significant ThermoTape sign test results, where 40 out of 47 subjects saw a decrease in pain when heat was used to remove ThermoTape, with only 1 subject reporting an increase in pain. Coupled with the statistically insignificant Tegaderm™ and KRT test

results, we can conclude that ThermoTape demonstrated a clinically noticeable decrease in pain when heat was applied before removal, and KRT and Tegaderm™ did not.

When focusing on the clinically relevant conditions, there is a statistically significant difference between ThermoTape the way it was designed to be used (heated upon removal) and Tegaderm™ the way it is used clinically (no heating upon removal). The pain difference between the two is 1.05. This is over the clinically significant threshold of 1 for children, therefore children are expected to feel the difference clinically. This does not exceed the clinically significant threshold of 1.2 for the general population, but it is close, so many patients will feel this difference clinically. ThermoTape had a higher pain value when removed without heat than Tegaderm™ with or without heat and so it likely had higher skin adhesion than Tegaderm™ over the 24-hour period.

ThermoTape had statistically significant results for reducing redness from tape removal when heat was applied, reducing redness by 45%. This indicates that ThermoTape with heat can not only reduce pain, but potentially reduce MARSI. Tegaderm™ exhibited a 23% increase in redness, and KRT a 4% increase in redness when heat was used. While these were not statistically significant results, they indicate that redness possibly increased with heat on these tapes. As they are not temperature sensitive, the redness could result from warming of the skin with the heat pack instead of irritation or erythema. Despite this possible baseline increase in skin redness with heating, ThermoTape still exhibited a significant reduction in redness with heat. ThermoTape with heat had an average redness of 0.48, while KRT without heat had an average redness of 0.43 on the 0-4 scale. The associated paired t-test p-value is 0.69, so there is not a statistically significant difference in redness from removal between the way ThermoTape should be

used (with heat), and the way KRT should be used (without heat). This indicates that ThermoTape has a comparative low-trauma release compared to KRT, which is a silicone tape specifically designed for low-trauma release. However, redness from KRT removal was not expected, as silicone adhesives are typically associated with the absence of skin redness [76]. While 0.43 is low on the redness scale, the elevated temperatures in Seattle during the trial could have trapped sweat under the tape, which could have contributed to the observed redness.

As expected, ThermoTape and Tegaderm™ exhibited less wear than KRT, as KRT is a low adhesion silicone tape. ThermoTape and Tegaderm™ did not have a statistically significant difference in wear. This was unexpected, as ThermoTape was made on a 4.5µm PET film backing, a stiff clear polymer which lacks stretchability when compared to the more stretchable Tegaderm™ polyurethane backing, which has a high moisture vapor transmission rate (MVTR), as shown in Table 4.1. While MVTR should not be a big differentiator between Tegaderm™ and ThermoTape, as the MVTR of ThermoTape is limited by the PSA film and not the 4.5µm PET backing, PET lacks the stretchability that Tegaderm™ has. Given the difference in stretchability, it is surprising to see similar wear results for ThermoTape and Tegaderm™ but encouraging. It is likely that in a long-term wear study, this difference in stretchability will become more of a factor.

The heat wave was a factor for this clinical trial. 13 subjects had sweat reported on their activity logs, under their tape samples upon removal, or had sweaty arms on tape application. Given that Seattle was amid a heat wave, a high MVTR was important to prevent moisture accumulation under the tape. The study was completed during the month of July 2022 with outdoor temperatures ranging from the high 70s to 90s

Fahrenheit (21 to 32˚C) over the 3 weeks of the study. There were three cases in which tape samples fell off subjects, and they all occurred in the last week of the study, where high temperatures ranged from 89˚F to 93˚F (32 to 34˚C). Despite the limitation of PET, ThermoTape did not have a statistically significant difference in wear when compared to Tegaderm™. Considering the higher average pain of ThermoTape without heat compared to Tegaderm™, and the similar average wear values of ThermoTape and Tegaderm™, ThermoTape likely has slightly higher skin adhesion than Tegaderm™. This stronger skin adhesion is desired, as it enables stronger attachment of wound care dressings or critical medical devices to the skin, which could decrease accidental dislodgement. Dislodgement of a wound care dressing would expose the wound and could lead to infection, and dislodgement of a medical device like a P/IV line could lead to severe medical complications. Having higher adhesion without the associated risk of MARSI would add value to the healthcare system.

One of the trial benchmarks, KRT, had low pain and redness values in the trial, but experienced the most wear among the three tapes. This was expected, as KRT is a low-adhesion silicone-based tape. In a comparative study with KRT and standard higher adhesion tapes with 200 nurses, 75% were dissatisfied with KRT due to unreliable adherence [76]. A recent 2019 study showed there is little evidence that silicone tapes are gentler on skin than microporous tapes, with many studies funded by 3M™ having small sample sizes and short wear duration [77]. These low-adhesion tapes like KRT are associated with a higher risk of device dislodgement, which was reflected in the high wear values during the trial [2,12]. Given the risk of device dislodgement, nurses often choose

higher adhesion tapes, leading to a higher risk of MARSI, reserving KRT for only the highest risk patients.

The other trial benchmark, Tegaderm™, was cut into strips instead of applying the entire dressing so that all three tapes would be the same size, and Tegaderm™ and ThermoTape would have a similar appearance. Tegaderm™ has been used on all age groups and has proven to be more effective than other medical tapes at securing wound care dressings and IV lines [78]. As stated in the European Wound Management Association (EWMA) position document Pain at Wound Dressing Changes: removing dressings should be done in a way that avoids unnecessary wound manipulation and prevents damages to the healing structures in and around the wound [79]. Tegaderm™ without heat had higher redness and pain than ThermoTape with heat and performed similarly to ThermoTape in wear. This indicates that ThermoTape may perform better than Tegaderm™ at maintaining wound integrity during dressing changes.

Ultrathin 4.5µm PET was used for the ThermoTape backing. However, the industry standard is thicker, nonwoven PU, which is used for Tegaderm™. Our prototype tape was made on PET for this clinical trial as it is simpler to do so since the PSA can be directly coated and dried on the PET backing. Ultrathin PET is a suitable short-term substitute for PU ThermoTape clinical testing. Future plans include making ThermoTape with a PU backing that is preferred for covering wound care dressings or P/IV lines for long-term wear. Because our PSA can be coated and dried on a liner and easily transferred to PU using a commercial laminator, future ThermoTape prototypes will be fabricated in a pilot roll-to-roll manufacturing facility. A limitation is that although the participants were

considered blinded, KRT is visibly distinctive from ThermoTape and Tegaderm™, so participants could be familiar with the product.

Special consideration was given to lean manufacturing methods. Each process was reviewed for opportunities to reduce time and budget consumption. Documentation, collaboration between researchers, continual dimensional analysis, cycle time analysis, advanced preparation of substrate materials, and overlap of independent processes were implemented towards the goal of an efficient and precisely repeatable fabrication. This process was rewarded with consistent AFM and peel testing results.

AFM and peel force results indicate improvements in ThermoTape from the previous ThermoTape publication [20]. The average reduction in peel force from 35°C to 45°C is higher, which is coupled with a slight size increase in the average phase-separated nanometer-sized domains with a tighter standard deviation. This is paired with generally small standard deviation values, when comparing lab-scale ThermoTape prototypes with 3M™ products. ThermoTape had similar average pain standard deviation values when compared to Tegaderm™, suggesting that the ThermoTape batches used in this trial were consistently fabricated.

4.5 Kenvue and ThermoTape comparison pilot study

The ThermoTape team engaged with Kenvue, who requested a comparative test with two of their products specifically on subject hands. The study report is outlined.

BAND-AID® Sensitive Skin and Water Block extra-large bandages were compared against ThermoTape in a 24-hour pilot study. This was done to compare with two standard adhesives, a low and high adhesion bandage, upon request of Kenvue.

Exclusion Criteria

Patients with cutaneous anomalies on test site: sunburns, infections, scars, moles, etc.

Patients with a history of eczema, adverse reactions to adhesives or recent history of dermatitis or skin reactions.

Materials

Water Block and Sensitive Skin BAND-AIDs were prepared so that the adhesive section could be tested without the dressing, as shown in Fig. 4.14.

1. Cut bandage in half while leaving the release films intact
2. Peel back and cut gauss section off while leaving the release film intact
3. Make short corner radius cuts through adhesive, backing, and release film to round the corners
4. Remove outer adhesive and backing from release liner and discard
5. Ready to apply

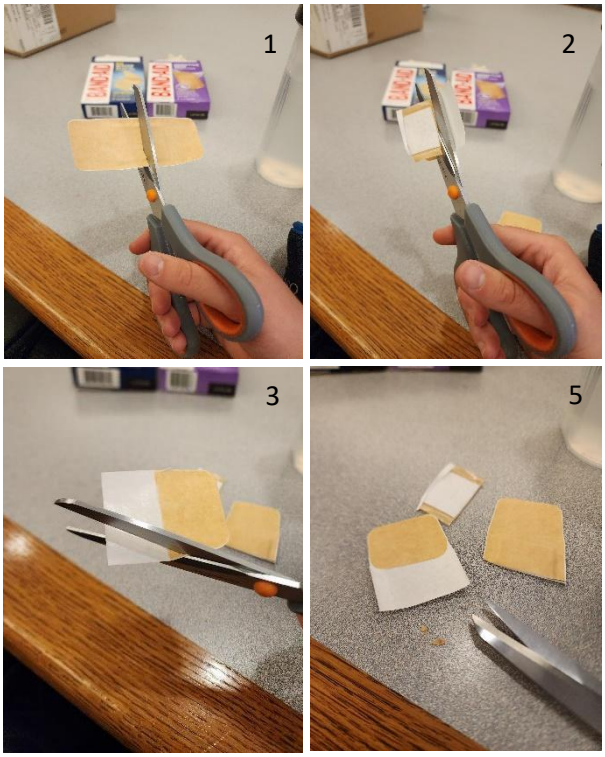


Fig. 4.14: BAND-AID preparation

ThermoTape was cut into 1’’x 2’’ strips, with a liner to assist with application. Corners were rounded.

Before tape application, the back of each hand was cleaned using a 70% isopropyl alcohol prep pad (Clever Health, Mansfield, Massachusetts, USA), with one wipe used per hand. Tape placement location was randomized, with one piece of ThermoTape on each hand, and one BAND-AID sample on each hand, as shown in Fig. 4.15. After each application, a finger was used to rub the tape on the forearm to ensure that the tape was fully adhered. Subjects were instructed to “proceed how you normally would with a BAND-AID on your hand”. Hand washing, showering, working out, and other activities were all permitted, with no requested restrictions.

Fig. 4.15: Tapes after application. Sensitive Skin is the darker sample at the bottom of the image, Water Block is the lighter colored sample at the top of the image, and ThermoTape is the two clear transparent tapes.

Subjects returned 24 hours later for removal. Wear data was collected, and pictures taken prior to removal. Wear data was collected with Table 4.3 from the clinical trial. An image taken prior to removal after 24 hours of wear is shown in Fig. 4.16.

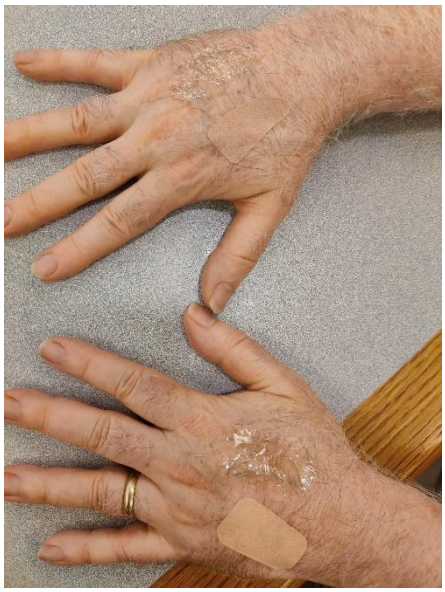


Fig. 4.16: Subject prior to removal and after 24 hours of wear

A visual pain scale of 0-10 (Fig. 4.7 from the clinical trial) was placed in front of the subject, and the removal process began. The removal order was randomized. After each piece was removed, the subject would be asked to report their pain on the 0-10 scale. Removal was initiated at an already lifted corner, or if all corners were adhered, a corner was lifted, and the tape was peeled at 180° at a constant rate. The peel rate depended on the strength of the adhesion. If adhesion was high, the tape was peeled slower to avoid skin tears. If adhesion was low, the peel rate was faster. If a hair was encountered, the tape was removed following the root of the hair to the tip.

A Dynarex™ Instant Hot Pack (Dynarex Corporation, Orangeburg, New York, USA) was applied to ThermoTape removal. The heat pack was activated and kneaded for one minute before application and applied to the tape for 30 seconds before removal. Each piece was removed immediately after warming.

Results and discussion

The wear and pain averages are shown in Table 4.5 below.

	Average Pain	Standard Dev	Average Wear	Standard Dev
Sensitive Skin	1.9	1.52	6.4	0.89
Water Block	4.2	2.39	6.6	0.55
ThermoTape	2.5	1.15	6.5	0.71

Table 4.5: Pain and Wear averages for Kenvue study

Table 4.5 shows that Sensitive skin had the most wear after 24 hours, followed by ThermoTape and Water Block. All three of these values are similar, within 0.1, with Water Block having the least wear. This indicates that ThermoTape performed well in a high wear environment with regular hot water exposure. Like the clinical trial, the ThermoTape standard deviation values are similar to industry tapes, highlighting the quality and consistency of ThermoTape fabrication.

The pain results in Table 4.5 show similar results to the wear, which is expected in adhesive clinical testing. Sensitive Skin had the lowest pain, shortly followed by ThermoTape, with Water Block having the highest self-reported pain. Water Block had one subject report a 7 on the pain scale, with many hairs pulled during removal, with the resulting removed bandage shown in Fig. 4.17 below. This data suggests that ThermoTape provides similar holding power to Water Block, the high adhesion tape, while providing pain closer to the low adhesion tape, Sensitive Skin. The ThermoTape pain values from this study were higher than usual. Previous pilot tests and clinical trials have been on younger patients under 30. This study had two patients older than 60 with significant hair on their hands. For these two older men this hair may have been a primary

or secondary factor for higher pain scores. This was our first time testing ThermoTape on the backhand, which has more hair than forearms. We have tested on the forearm as it is a standard location for adhesive testing due to the limited presence of hair [49]. Future clinical testing will stick to the forearms. The team plans to complete this study again on forearms once ThermoTape has been fabricated on polyurethane.

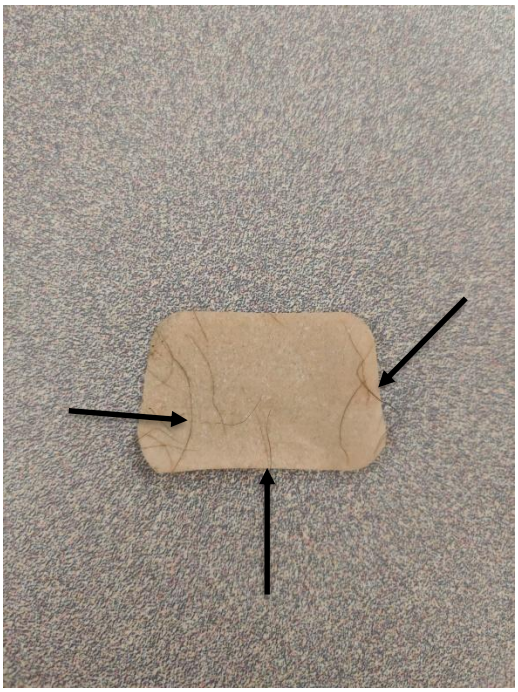


Fig. 4.17: Removed Water Block adhesive with hairs, a few indicated by arrows.

Chapter 5: Refinement, new product development, and testing

5.1. Motivation

While existing high adhesion tapes have reached the ceiling for adhesion levels as they already cause MARSI upon removal, ThermoTape can exceed this limit, as high skin adhesion levels can be reduced upon removal. As a result of our I-Corps™ interviews, the ThermoTape product requirements have been updated to have higher adhesion than our competitor, Tegaderm™, at skin temperature. There are situations where stakeholders would want a product that has higher adhesion than Tegaderm™ at skin temperature with a low release (adhesion levels 10-20% above KRT adhesion levels), and a product that is equivalent to Tegaderm™, with a very low release (adhesion levels around KRT adhesion levels). Higher adhesion use cases would be on patients at high risk of device dislodgment, such as with confused patients and active children [2,3]. Additionally, a thicker PSA is expected to increase the wear performance, allowing for longer-term wear. High adhesion, matching current Tegaderm™ levels, use cases would be patients at extreme risk of MARSI, who need the gentlest release possible while also allowing for secure device attachment [2,3]. The gentlest release possible is adhesion levels seen by KRT. These relative adhesion levels are shown in Table 1.1 and Fig. 5.2, which describe industry standard tapes and our testing results from these tapes in comparison with ThermoTape. Currently, patients that require gentle release, such as burn victims, are left with low adhesion tapes as their options, often leading to device or wound dressing dislodgment. In these studies, ThermoTape was compared against Tegaderm™ and KRT, which are high and low adhesion tapes. The motivation of this was

to compare ThermoTape with the standard high adhesion tape when considering wear performance. Including a low adhesion tape, KRT, as a benchmark allows for comparison of ThermoTape removal with heat with a gentle release silicone adhesive.

Refinement focused on transitioning to a hospital setting. Prior clinical testing had been done outside of the hospital. In a hospital, we will need to have the adhesive applied longer, use their heat pack protocol, and be confident that our results will be positive before progressing to a hospital pilot study. These needs were addressed with a series of three pilot tests.

5.2. PSA thickness variation

5.2.1. Background

The adhesion level of medical tapes can be controlled within a range specific to each PSA with the thickness of the coated film [80]. We want limited wear during long-term wear and adhesion levels greater than Tegaderm™, while also having an injury-free release. To test this, we created prototypes with varying PSA thicknesses, as we look to refine the adhesion level and test two potential future products.

5.2.2. Heat pack considerations

With a thicker adhesive layer, the TSP at the skin-PSA interface is more insulated from the heat pack. A 100µm PSA film coupled with the usual 4.5µm PET backing has nearly double the thickness of a heat insulative material to heat to reach the nanodomains that must be melted to initiate release. That means it is likely that more heat is required to melt the TSP nanodomains, requiring longer heat pack application.

5.3. Additional materials and methods

5.3.1 Tape fabrication

Tape was fabricated with a similar procedure that was outlined in Chapter 4. Tape used for in vitro verification, including peel testing, AFM, and profilometry, was fabricated on 50µm PET. Tape used for pilot testing on skin was fabricated on 4.5µm PET. Every fabricated sheet used in clinical testing was verified with peel testing. Several different PSA thicknesses were fabricated, including 25µm, 50µm, and 100µm. Pure PSA (no temperature sensitive additive, just AH-115) was fabricated first to demonstrate the concept of coating different thicknesses, followed by 1%TSP ThermoTape. Tapes were fabricated with the die head clearance and dispense rates outlined in Table 5.1, with a stage speed of 6cm/min for all coatings.

Table 5.1: Die head clearance and dispense rates to coat 25µm, 50µm, and 100µm thick PSA films.

	Die Head Clearance [mm]	Dispense Rate [µl/min]
Original Prototype	0.203	600
Double Thickness	0.406	1200
Half Thickness	0.102	300

5.3.2 Profilmetry

Coating thickness was measured by attaching the sample substrate to a double-sided adhesive backing that was fixed to the Olympus OLS4100 optical profilometer stage. The scan area was located using the 5x magnification objective and the vertical scan bounds were set with the 20x magnification objective. The scan was conducted using the 20x

magnification objective and the LEXT OLS4100 software was used to measure five sets of points to calculate the coating height relative to the substrate.

5.3.3. Pilot study designs

Several pilot studies were conducted on five subjects to further refine the design, demonstrate long-term wear, test different PSA thicknesses, and to prepare for clinical testing at HMC.

5.3.3.1 First pilot study

The first pilot study was a 7-day study to evaluate ThermoTape performance as a long-term wear (over 7 days) tape in comparison to Tegaderm™. Tape application was on Day 0, and tape removal was on Day 7. ThermoTape and Tegaderm™ were applied to patients' forearms. Subjects sent pictures of their forearms to the researchers on Days 1, 3, and 5. ThermoTape was removed with heat, and Tegaderm™ without heat to only test clinically relevant conditions. Pain was self-reported and collected. Quantifiable outcomes were comparing ThermoTape and Tegaderm™ wear performance and pain during removal.

First, the forearm underside area was cleaned using an isopropyl alcohol wipe. Following the pre-tape application preparations, ThermoTape (1 by 2 inches), was applied horizontally, in vertical succession on the forearm. After each application, a finger was used to rub the tapes in a vertical motion to ensure that the tape, especially edges, were fully adhered. The first area of tape application was 2 inches distal the wrist, the second 2 inches distal the closest edge of the first piece of tape, and the third piece 2 inches

distal the closest edge of the second piece. To eliminate variability, the positions of the tapes were randomized from subject to subject.

When subjects returned to have the tapes removed on Day 7, they waited in the room for 30 minutes to acclimate. The wear of the tape was recorded with the scale above in Table 4.3 prior to removal. Then they were given the Wong-Baker pain scale in Fig. 4.7 so that they could self-report pain after each piece of tape was removed. A Dynarex heat pack was used for tape removal. Prior to heat pack activation, the corner of each sample was lifted. The heat pack was activated and kneaded for one minute before application onto the subject's skin. Then the heat pack was applied to ThermoTape for 30 seconds before removal was initiated. A separate heat pack was used for the second piece of ThermoTape. Heat was not used for Tegaderm™ removal.

5.3.3.2 Second pilot study

The second pilot study was designed based on the results of the first pilot study and input from HMC. It was performed to refine the heat pack application time for thicker, 100µm ThermoTape and to test the Cardinal Health Instant Heat Pack used by HMC. One forearm had three pieces of 100µm ThermoTape, which were removed after 24 hours with a Dynarex heat pack applied for 30, 45, and 60 seconds. The other forearm had one piece of 50µm and 100µm ThermoTape, which was removed after applying the Cardinal Health heat pack for 30 seconds. Tape was applied similarly to the first pilot study above. The removal process was similar as well, other than the variation in heat pack application times, and using the Cardinal Health Instant Hot Pack for the other arm.

5.3.3.3 Third pilot study

The final pilot study was conducted to analyze the effect of a 50µm thick paper towel thermal barrier on ThermoTape removal. Three pieces of 50µm thick ThermoTape on 4.5µm PET backing were applied to the left or right arm, which was randomized. On the other arm, one piece of 50µm ThermoTape on 4.5µm PET backing was applied to the middle of the forearm. Subjects wore the tape for 24 hours and were not given any instructions or limitations on what they could or could not do. When subjects returned 24 hours later, they waited at least 30 minutes in the room to acclimatize. Wear was recorded and pictures were taken prior to removal. One corner was slightly raised on each tape, and then Dynarex heat packs were activated by popping and then shaking for 60 seconds, and a paper towel was placed as a thermal barrier over the tape and between the patient and heat pack. The heat pack was applied for 30, 45, and 60 seconds before removal. The removal order and locations were randomized for the different heat pack application times. The paper towel thickness was measured with electronic calipers. Tapes were removed after their warming period, and pain was self-reported using our standard Wong-Baker pain scale in Fig. 4.7. Tape on the other forearm was removed with the Cardinal Health Instant Hot Pack. This heat pack was activated by popping and then shaking for 60 seconds, and then applying to the skin-attached tape for 60 seconds without a thermal barrier. The tape was then removed, and the pain score collected. While the heat pack was being applied, a video was taken with a FLIR ONE series Thermal Camera with the FLIR ONE App on an iPhone to characterize the temperature of the heat pack and the skin after tape removal.

5.4. Results

5.4.1. Profilometry

Profilometry was used to verify that the expected thicknesses were coated. Table 5.1 above with the three die head clearances and associated dispense rates were first tested with pure PSA. Three measurements were taken per film. Table 5.2 shows the profilometry data for the pure PSA at different die heights.

Table 5.2: Optical Profilometry Results for Pure PSA Samples

Die Height [mm]	Average Measured Thickness [µm]	Standard Deviation [µm]
0.102	27.64	2.93
0.203	58.66	5.55
0.406	105.18	6.95

The intended PSA thicknesses were 25µm, 50µm, and 100µm. Once the thicknesses were within 10µm of the expected value, we fabricated 1% TSP samples. Table 5.3 shows the profilometry data for 1% TSP ThermoTape at different die heights.

Table 5.3: Optical Profilometry Results for 1% TSP Samples

Die Height [mm]	Average Measured Thickness [µm]	Standard Deviation [µm]
0.102	34.18	0.49
0.203	60.21	2.15
0.406	110.8	2.56

5.4.2. Peel testing

Peel testing results for pure PSA at different thicknesses in comparison with KRT, Durapore™, and Tegaderm™, are shown in Fig. 5.1 and Table 5.4 below. Three samples for each data point were taken, with ThermoTape samples fabricated on 50µm PET backings.

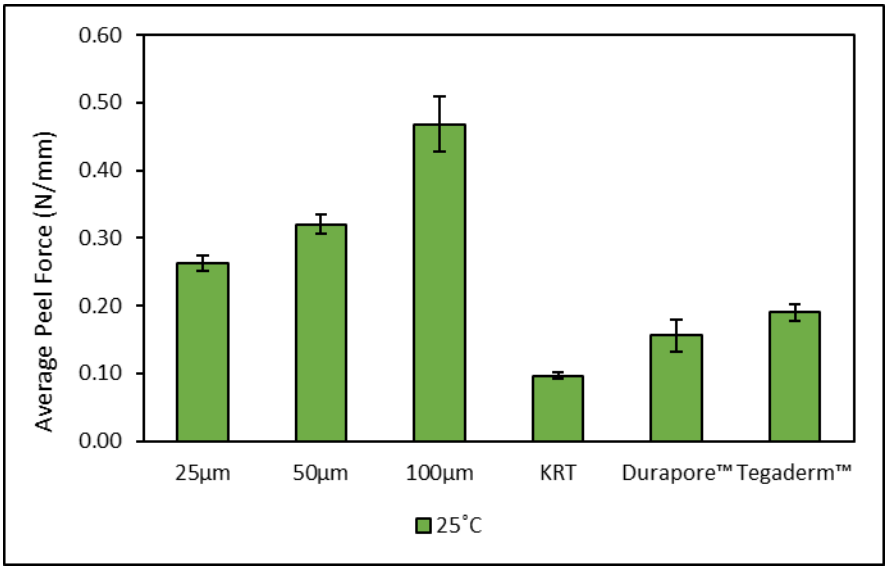


Fig. 5.1: Peel testing results for pure PSA at different thicknesses in comparison with KRT, Durapore™, and Tegaderm™

Table 5.4: Peel testing results for pure PSA at different thicknesses in comparison with KRT, Durapore™, and Tegaderm™

Tape	Peel Force at 25˚C (N/mm)	Standard Deviation
25µm ThermoTape, Pure PSA	0.263	0.0120
50µm ThermoTape, Pure PSA	0.320	0.0140
100µm ThermoTape, Pure PSA	0.468	0.0410
KRT	0.0970	0.0050
Durapore™	0.156	0.0230
Tegaderm™	.190	0.0120

The peel force increases with ThermoTape thickness. From 25µm to 50µm, there was 21.67% increase in adhesion. From 50µm to 100µm, there was a 46.25% increase in adhesion. From 25µm to 100µm, there was a 77.95% increase in adhesion. KRT, Durapore™, and Tegaderm™ were tested to serve as benchmarks.

Peel testing results for ThermoTape (with 1% TSP) are shown in Fig. 5.2 and Table 5.5 below. Three samples for each data point were characterized, with ThermoTape samples fabricated on 50µm PET backings.

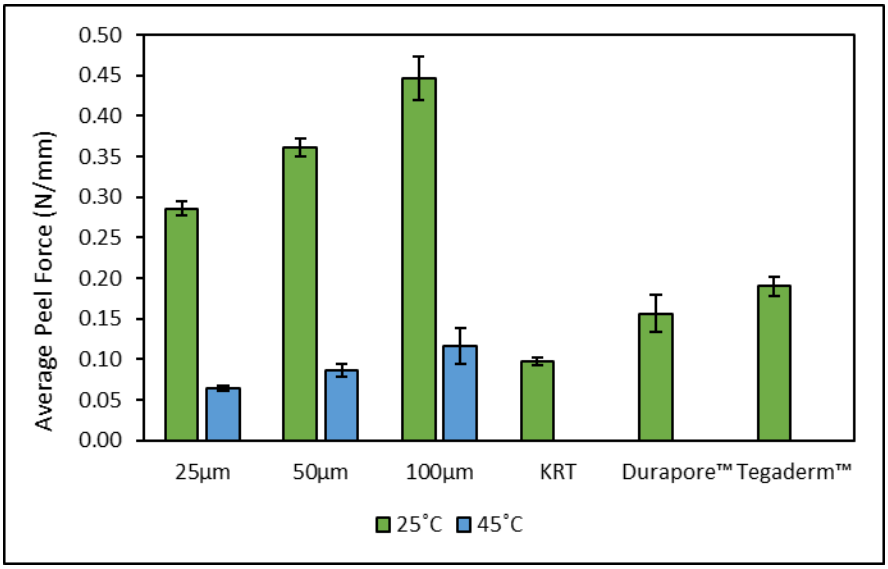


Fig. 5.2: Peel testing results for ThermoTape (with 1% TSP) at 25ºC and 45ºC in comparison with KRT, Durapore™, and Tegaderm™ at 25ºC.

Table 5.5: Peel testing results for ThermoTape (with 1% TSP) at 25ºC and 45ºC in comparison with KRT, Durapore™, and Tegaderm™ at 25ºC with % change in adhesion.

ThermoTape Thickness	Peel Force at 25˚C (N/mm)	Peel Force at 45˚C (N/mm)	% Change in Adhesion
25µm	0.286	0.064	77.6
50µm	0.361	0.087	75.9
100µm	0.446	0.117	73.8
KRT	0.0970	N/A	N/A
Durapore	0.156	N/A	N/A
Tegaderm	.190	N/A	N/A

This data shows that all three thicknesses exhibited over a 70% reduction in adhesion when heated from 25ºC to 45ºC, which is the product requirement used for verification for clinical testing. The peel force increases with thickness for samples removed at 25ºC and 45ºC. From 25µm to 50µm, there was 26.3% increase in adhesion at 25ºC, and a 35.9% increase in adhesion at 45ºC. From 50µm to 100µm, there was a 23.55% increase in adhesion at 25ºC, and a 34.48% increase in adhesion at 45ºC. From 25µm to 100µm, there was a 55.94% increase in adhesion at 25ºC, and an 82.81% increase in adhesion at 45ºC. 25µm ThermoTape had a 77.6% decrease in peel force when removed at 45ºC and compared to 25ºC, while the 50µm and 100µm ThermoTape had a 75.9% and 73.8% decrease, respectively.

KRT, Durapore™, and Tegaderm™ were tested as well to serve as benchmarks. All three ThermoTape thicknesses exhibited higher adhesion then KRT, Durapore™, and Tegaderm™ at 25ºC. At 45ºC, all thicknesses exhibited lower adhesion than Durapore™ and Tegaderm™. 25µm and 50µm ThermoTape exhibited lower adhesion than KRT at 45ºC.

5.4.3. Atomic force microscopy

Fig. 5.3 shows AFM phase images for 25µm, 50µm, and 100µm ThermoTape, and Table 5.6 shows the nanodomain size and concentration. This shows similar surface concentration for 50µm and 100µm ThermoTape, with 25µm having a higher TSP surface concentration. 25 µm has a 77.52% higher surface concentration than 50µm ThermoTape.

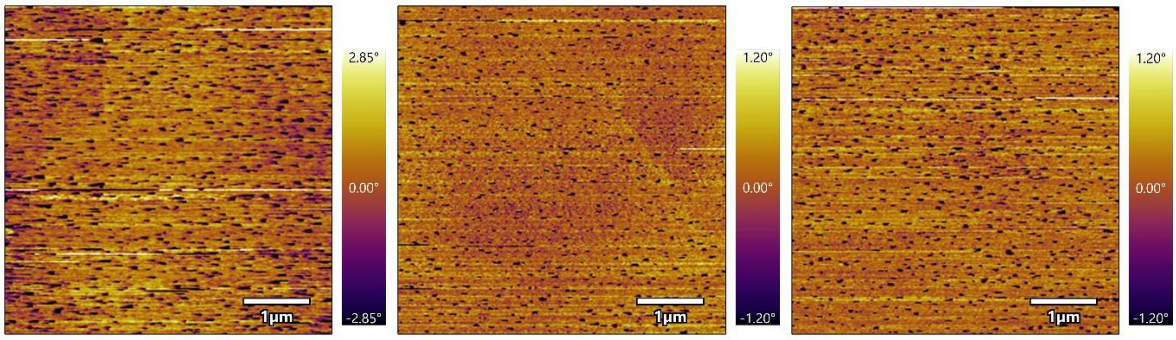


Fig. 5.3: AFM phase images 1%TSP ThermoTape samples with the following PSA thicknesses: 25µm (left), 50µm (middle), and 100µm (right). Areas of low phase (dark) correspond to TSP nanodomains.

Table 5.6: TSP nanodomain CE diameter and surface area for 25µm, 50µm, and 100µm ThermoTape from Fig. 5.3.

ThermoTape Thickness	CE Diameter (nm)	Standard Deviation (nm)	Surface Area (nm^2)	Standard Deviation (nm^2)
25µm	44.4	30.9	2290	3030
50µm	36.8	16.9	1290	1160
100µm	36.7	17.6	1300	950

5.4.4 ThermoTape pilot studies

5.4.4.1 First pilot study

The first pilot study was a 7-day study to test long-term wear of 50µm and 100µm ThermoTape in comparison with Tegaderm™. The first pilot test pain data is shown in Fig. 5.4. Tegaderm™ was removed without heat, and ThermoTape with heat to test only clinically relevant conditions.

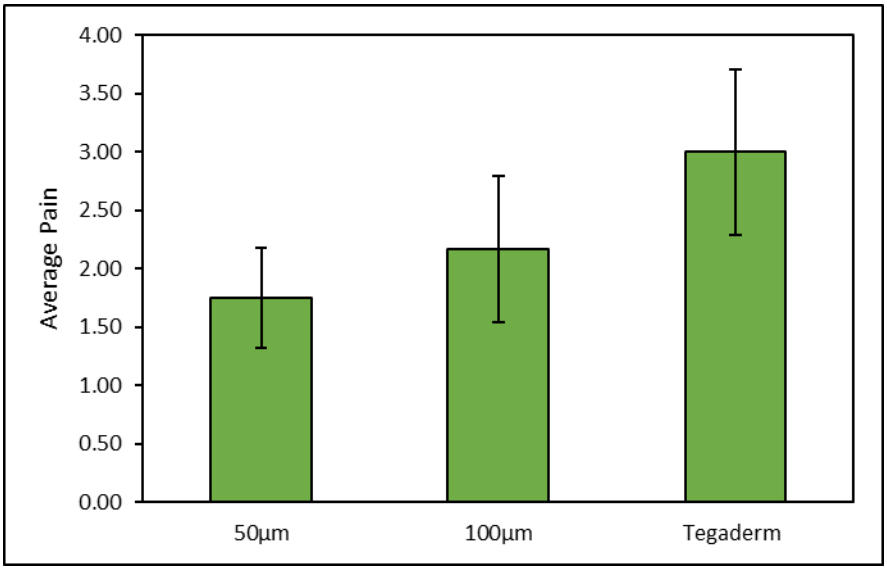


Fig 5.4: Average pain values of 50µm and 100µm ThermoTape removed with heat, and Tegaderm™ was removed without heat.

Fig. 5.4 shows that Tegaderm™ had the highest average pain score at 3.0, followed by 100µm and 50µm ThermoTape with heat release at 2.16 and 1.75, respectively. Fig. 5.5 below shows the average wear for the three tapes after 7 days, which were recorded with Table 4.3 from the clinical trial, where a 7 is no wear with all corners adhered.

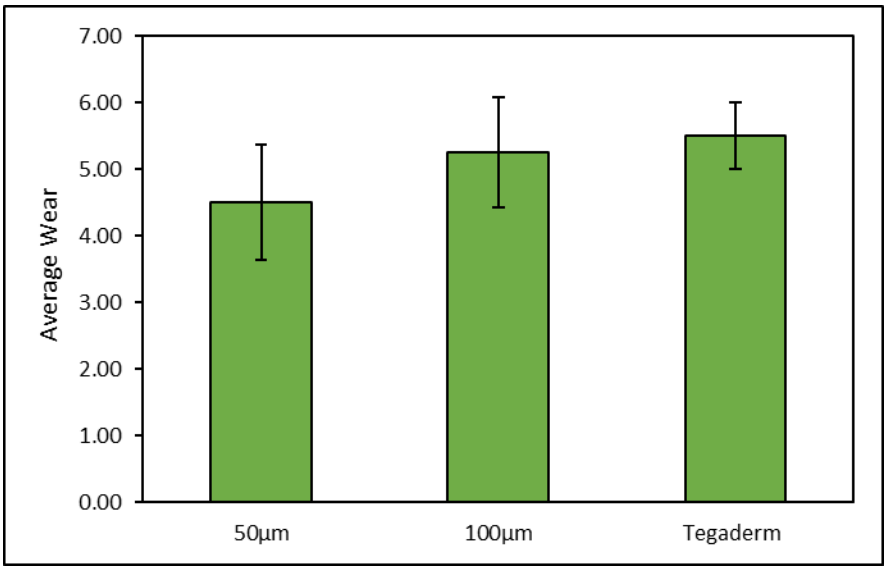


Fig. 5.5: The average wear for 50µm and 100µm ThermoTape and Tegaderm™ after 7 days of wear.

Fig. 5.5 shows that Tegaderm™ had slightly less wear than both ThermoTape samples, with Tegaderm™ at 5.5, and 100µm and 50µm at 5.25 and 4.5, respectively.

5.4.4.2 Second pilot study

The second pilot study was done to refine the heat pack application time for 100µm ThermoTape and to test the Cardinal Health Instant Hot Pack used at HMC. Fig. 5.6 shows the average reported pain for the three 100µm ThermoTape samples removed with the Dynarex heat pack applied for 30, 45, and 60 seconds.

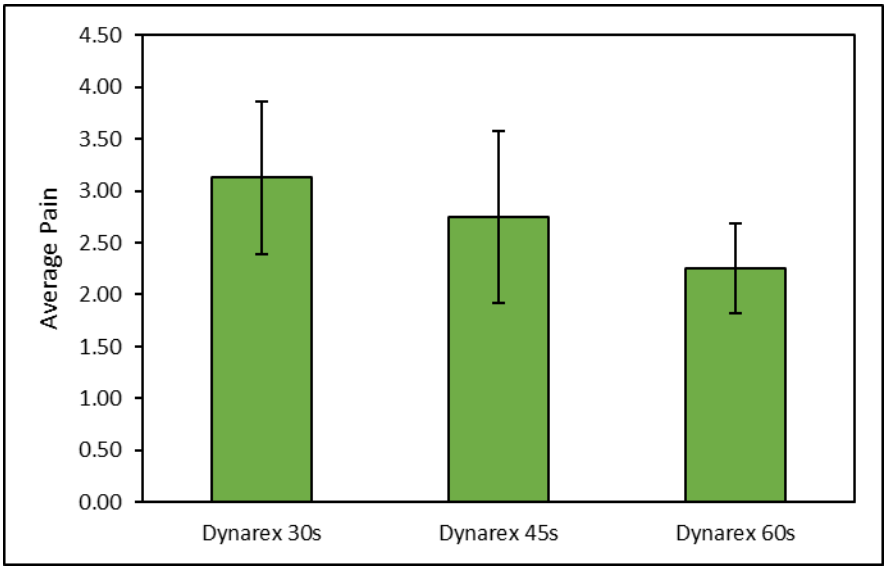


Fig. 5.6: Average pain for the three 100µm ThermoTape samples removed with a Dynarex heat pack applied for 30, 45, and 60 seconds.

The average reported pain score was 3.12 for 30 seconds, 2.75 for 45 seconds, and 2.25 for 60 seconds. The wear of these tapes after 24 hours of wear is shown in Fig. 5.7.

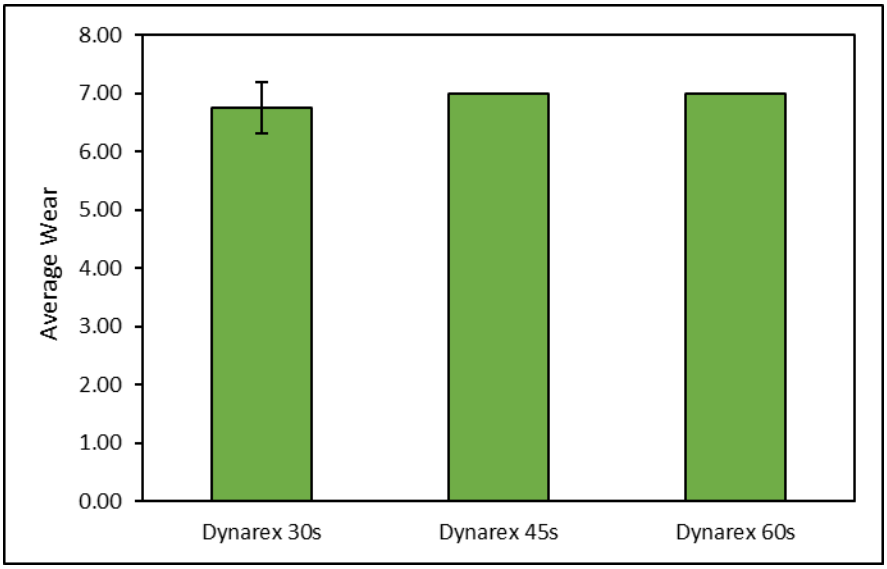


Fig. 5.7: Average wear of three 100µm ThermoTape samples after 24 hours of wear.

The wear for the 30 second samples was 6.75, and 7 for the 45 and 60 second samples. This gives an overall wear average of 6.92 for 100µm ThermoTape with 24 hours of wear.

The pain data from the other forearm, which had one piece of 50µm and 100µm ThermoTape and was removed by applying the Cardinal Health heat pack for 30 seconds without a thermal barrier, is shown in Fig. 5.8.

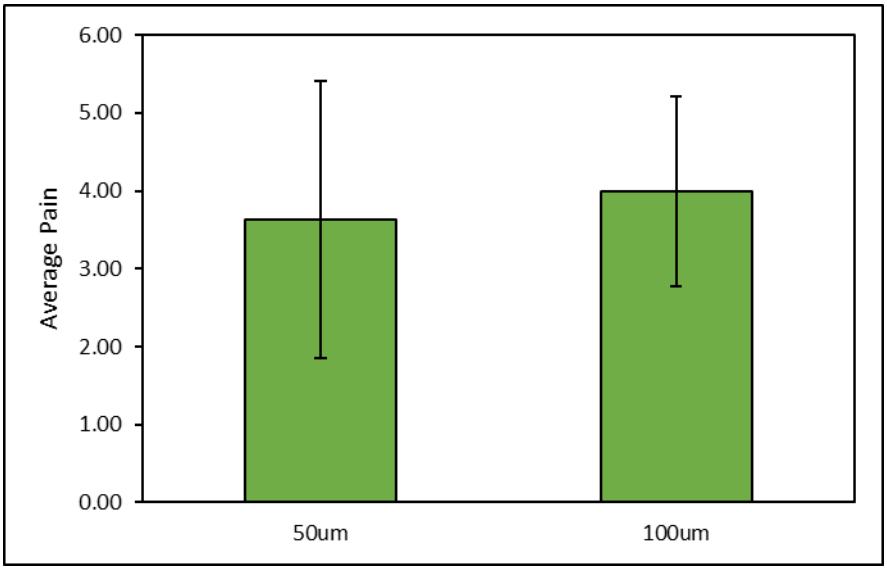


Fig. 5.8: Average pain of 50µm and 100µm ThermoTape removed by applying the Cardinal Health heat pack for 30 seconds without a thermal barrier.

The average pain for the 50µm ThermoTape samples removed by applying the Cardinal Health heat pack for 30 seconds was 3.62, and 4.0 for 100µm. The associated wear values are shown in Fig. 5.9 below.

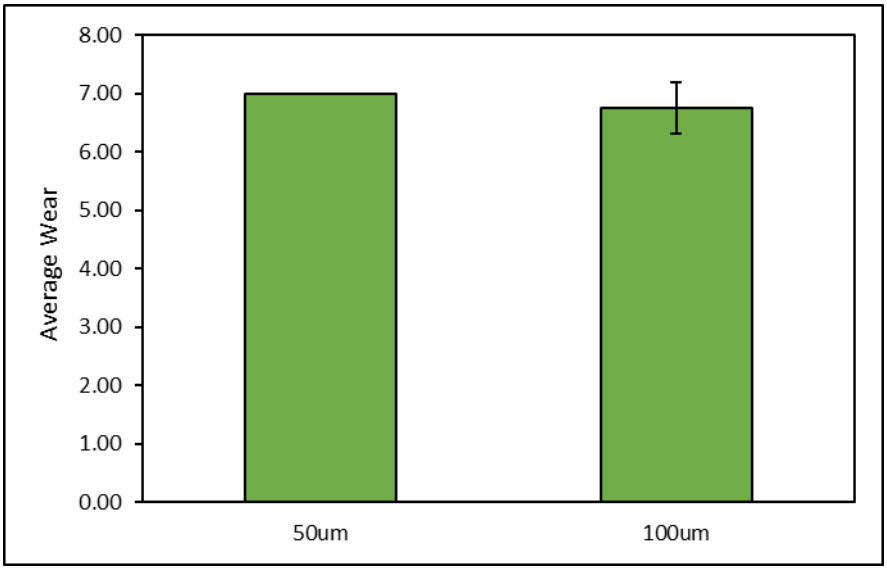


Fig. 5.9: Average wear of 50µm and 100µm ThermoTape after 24 hours of wear

This shows a wear value of 7 for 50µm and 6.75 for 100µm ThermoTape after 24 hours of wear.

5.4.4.3 Third pilot test

The third pilot study was done to investigate the effect of a paper towel thermal barrier on ThermoTape removal and to test the Cardinal Health HMC heat pack with longer application times. 50µm ThermoTape was removed with a Dynarex heat pack that was applied for 30, 45, and 60 seconds with a paper towel thermal barrier, and a Cardinal Health heat pack that was applied for 60 seconds without a thermal barrier. Fig. 5.10 below displays the average pain data for the third clinical study. The average pain for 50µm ThermoTape was removed with a Dynarex heat packs dropped significantly when heat was applied longer. When the Dynarex heat pack was applied with a thermal barrier for 30 seconds, the average pain was 1.55, but when it was applied for 45 and 60 seconds, the average pain was .760 and .500, respectively. The Cardinal Health Instant Hot Pack that was applied for 60 seconds without a thermal barrier had an average pain score of 1.8.

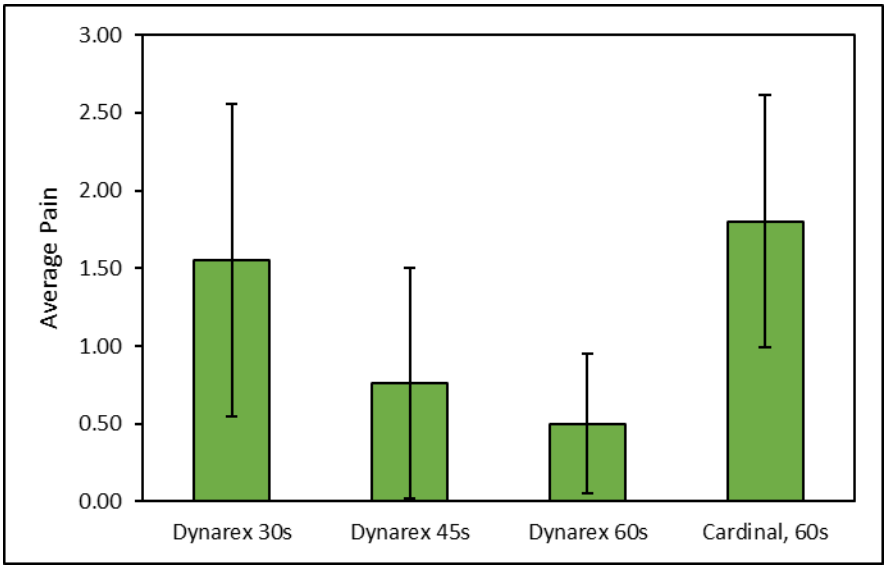


Fig. 5.10: Average reported pain of 50µm ThermoTape when removed with a Dynarex heat pack that was applied for 30, 45, and 60 seconds with a thermal barrier, and a Cardinal Health heat pack applied for 60 seconds without a thermal barrier.

Heat packs and skin temperatures in this pilot study were characterized with a FLIR thermal camera. The calibration images are shown in Fig. 5.11 below.

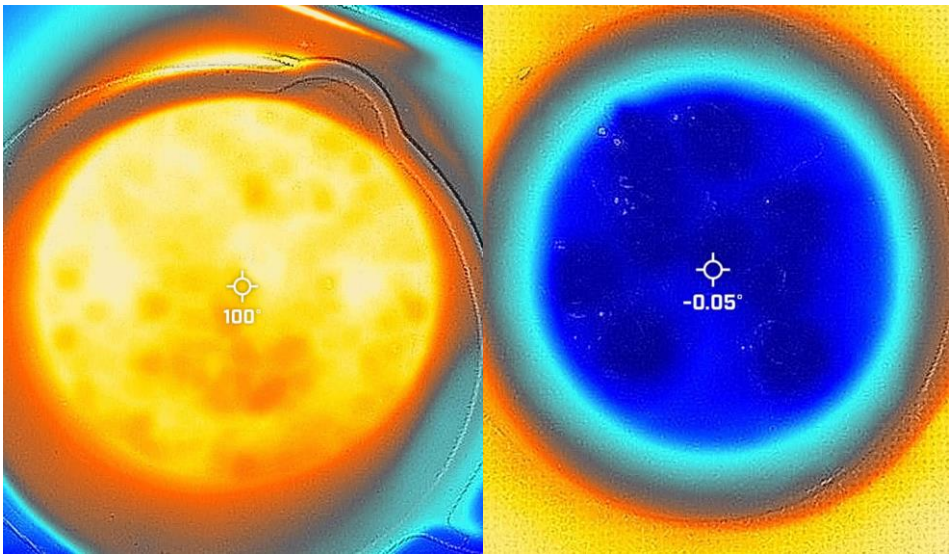


Fig. 5.11: FLIR thermal camera calibration images. Left shows boiling water with a measurement of 100ºC, and right shows ice water, with a measurement of -0.05ºC.

These calibration measurements were taken 10 times each. This data is shown in Table 5.7 below. The boiling water had an average of 100.63ºC, and the iced water had an average of -0.01ºC.

Table 5.7: Calibration measurements taken with the FLIR thermal camera on iced and boiling water.

	Theoretical Value	Average Actual Value	Standard Deviation
Iced Water	0°C	-0.01ºC	0.268ºC
Boiling Water	100°C	100.63ºC	1.15ºC

Thermal images taken during the study and the resulting data are shown in Fig. 5.12 below.

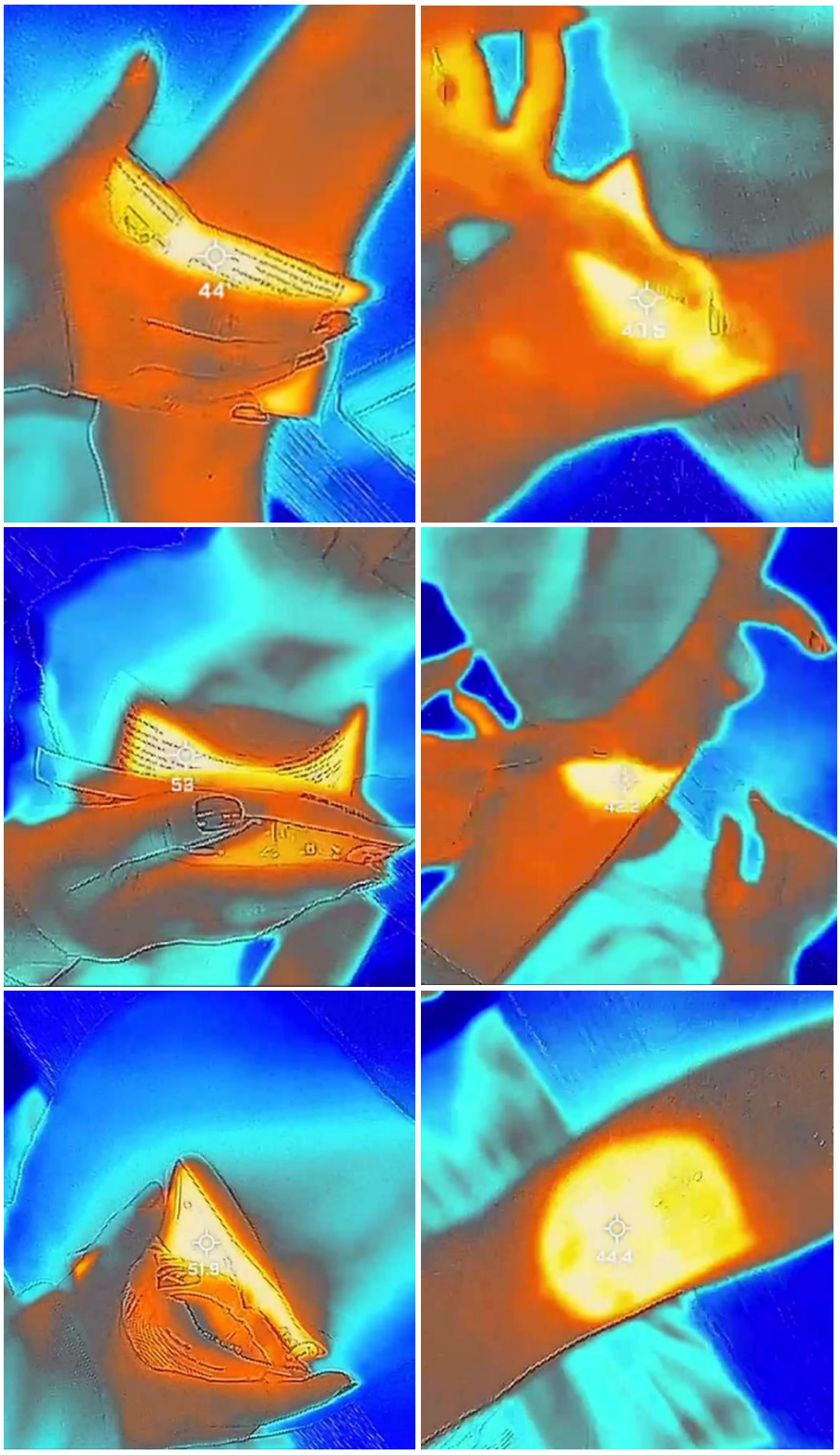


Fig. 5.12: FLIR thermal camera images.

The temperatures are visible in Fig. 5.12 in faint white text and are shown in Table 5.8 and are compared with the average pain values from Fig. 5.10. The top left shows the Cardinal Health heat pack during skin application for 60 seconds without a thermal barrier, showing a heat pack temperature of 44.0ºC. The top right shows the skin temperature immediately after the Cardinal Health heat pack was applied for 60 seconds and tape was removed. This shows a skin temperature of 40.5ºC. The middle left shows the Dynarex heat pack during skin application for 45 seconds with a thermal barrier, showing a heat pack temperature of 53ºC. The middle right shows the skin temperature immediately after the Dynarex heat pack was applied to the skin for 45 seconds and the tape was removed. This shows a skin temperature of 42.2ºC. The bottom left shows the Dynarex heat pack during skin application with a thermal barrier, showing a heat pack temperature of 51.9ºC. The bottom right shows the skin temperature after the Dynarex heat pack was applied to the skin for 60 seconds and the tape was removed. This shows a temperature of 44.4ºC.

Table 5.8: Heat pack temperatures when applied to skin, skin temperatures after heat pack application and tape removal compared with the average pain values from Fig. 5.10.

Condition	Heat pack temperature, ºC	Skin temperature, ºC	Average pain value (Fig. 5.10)
Cardinal heat pack, 60 seconds	44	40.5	1.88
Dynarex heat pack, 45 seconds	53	42.2	0.760
Dynarex heat pack 60 seconds	51.9	44.4	0.500

5.5. Discussion

5.5.1 In vitro characterization

Profilometry data in Tables 5.2 and 5.3 indicated that the thicknesses were around 10µm of the expected value, providing verification needed to progress to peel testing. Peel testing data for the pure PSA at different thicknesses in comparison with KRT, Durapore™, and Tegaderm™ yielded strong results. This study began with pure PSA data (Fig. 5.1 and Table 5.4), which showed that three thicknesses exhibited higher adhesion then KRT, Durapore™, and Tegaderm™ at 25ºC. It also provided relative adhesion values, with KRT being half the adhesion of Tegaderm™, as a low and high adhesion tape, relatively. Durapore™ and Tegaderm™ both increase in adhesion over time as an acrylic adhesive, while KRT does not, so for a longer wear, the adhesion levels for Tegaderm™ and Durapore™ would be higher than what was tested here. As an acrylic adhesive, the adhesion of ThermoTape should also increase over time. This data showed that the peel force increases with PSA thickness, indicating that the adhesion levels of future products can be modified for specific use cases based on the thickness of the coated PSA. Rough surfaces require a thicker adhesive to enable the PSA to flow into the valleys of the surface. Two DIN standard roughness parameters, R_a and R_Z, are typically considered when analyzing skin roughness. R_a is the arithmetic mean surface roughness and R_Z is the mean of the maximum peak to valley height in 5 sampling lengths. Edwards, et al, [81] analyzed the R_a and R_Z of skin in patients of all ages in areas that habitually exposed and habitually unexposed to the sun. R_Z values ranged from 59.4µm to 83.3µm in exposed areas (the back of the hand), and from 78.0µm to 151.3µm in unexposed areas (back of the buttocks). R_a values ranged from

13.3µm to 19.3µm in exposed areas, and 16.2µm to 38.9µm [81]. With R_Z values (maximum peak to valley heights) of over 50µm and even over 100µm, this indicates that a thicker PSA is needed to fully flow into the valleys of the skin. This is likely why adhesion increased with PSA thickness both in vitro and on skin.

Peel testing results for ThermoTape with and without the TSP additive (Fig. 5.1 and 5.2) yielded similar results for samples removed at 25ºC. The peel force values and increases in adhesion with increases in thickness were similar. The three ThermoTape samples were also tested at 45ºC. The peel force at 45ºC was less than the peel force of KRT (0.097 N/mm) for the 25µm and 50µm ThermoTape samples, while the 100µm ThermoTape sample was slightly higher at 0.117 N/mm. As our benchmark for low adhesion and a gentle silicone adhesion, achieving peel force less than KRT upon removal is a significant milestone, as it indicates that skin trauma from removal is likely to be low. The 100µm ThermoTape sample at 45ºC had slightly higher peel force than KRT, but it was still well below Durapore™ and Tegaderm™. This indicates it may be more painful than KRT for removal but will be less painful than Durapore™ and Tegaderm™.

The 25ºC peel force values for all three thicknesses of ThermoTape in Fig 5.2 indicate significantly higher peel force values than Tegaderm™ and Durapore™. 50µm ThermoTape had a peel force 90% higher than Tegaderm™ at 25ºC, and 100µm ThermoTape was 134% higher than Tegaderm™. Even 25µm ThermoTape had a 50% higher peel force than Tegaderm™. This indicates that all three ThermoTape thicknesses have higher adhesion than Tegaderm™ on an LDPE substrate, and may have higher adhesion on skin, offering higher holding power. This higher holding power

could potentially more strongly hold and secure critical medical devices to the skin, possibly reducing accidental device dislodgement rates. Even with current high adhesion medical tapes, device dislodgement is as high as 17.5% for IV lines [17]. As Tegaderm™ and other high adhesion medical tapes already cause significant rates of MARSI upon removal, as high as 13% in the general population, having adhesion higher than standard high adhesion tapes is not practical without an adhesion mitigation removal mechanism [6,7]. This peel force data has shown that 25µm and 50µm ThermoTape offer significantly higher adhesion than current high adhesion tapes when peel tested on LDPE substrates at 25ºC, while exhibiting peel force values under the standard low adhesion tape, KRT, when peel tested on LDPE substrates at 45ºC. If this translates in vivo, this could provide unprecedented secure device attachment with a low risk of MARSI, addressing an unmet need.

This was enabled by all three thicknesses seeing a significant change in adhesion when removed at 45ºC compared with 25ºC. The reduction in peel force when heat was used for removal was in the range of 73.8%-77.6The reduction in peel increased with PSA thickness. There was a 3.8% difference in adhesion between 25µm and 100µm ThermoTape, with 25µm exhibiting a larger reduction in adhesion with heat. This difference is small, however, this difference could be attributed to the AFM data in Fig. 5.3, where 25µm had a 77.5% higher TSP surface concentration than 50µm ThermoTape. The larger reduction in adhesion with heat of the 25µm ThermoTape could be due to the higher TSP surface concentration. As shown in our first publication and in Table 3.1, a larger surface concentration when coupled with small nanodomain size yields a larger reduction in peel force. Table 3.1 shows that a nanodomain size

around 30nm yielded the largest reduction in peel force. Samples with a larger surface area did not yield a larger peel force reduction if the nanodomain size was 77nm or higher. Our product requirement for ThermoTape verification before using a coated sheet in clinical testing has been a peel force reduction of 70% or more coupled with a nanodomain size of under 50nm. The 25µm sample is interesting as it achieves something we did not observe with the many other conditions we have tested. It has a surface concentration 77.5% higher than our 50µm sample, but it also achieves this while having a nanodomain size of less 50µm. This enabled a larger reduction in peel force upon tape warming, as these surface TSP nanodomains melt upon application of heat, forming a greater number of non-adhesive puddles on the skin-PSA interface, enabling easier release.

While 25µm has a higher TSP surface concentration and slightly larger nanodomain size, the TSP nanodomain sizes and concentrations are similar between 50µm and 100µm.This was not expected. Prior to this study, the team hypothesized that in a thicker ThermoTape (PSA+TSP) film, more TSP would migrate to the surface as there simply was more TSP in the film, resulting in a higher concentration of TSP on the surface and a larger drop in peel force upon application of heat. Instead, we saw 25µm with the largest surface concentration. A 100µm ThermoTape film has 4x the TSP content compared to a 25µm ThermoTape film at the same 1% TSP concentration. The team expected this 4x increase in TSP content to be visible on the surface, after solvent movement during film drying carries growing TSP particles towards the surface and deposits them on the PSA surface, as shown in Fig 3.6. This AFM and peel testing data has shown that this is not the case, indicating that the TSP that makes it to the surface

likely comes from the near surface. Given that 25µm ThermoTape has similar TSP surface concentration as 100µm ThermoTape, we can hypothesize that the surface TSP on a dried ThermoTape film comes from a depth of less than 25µm. While the 100µm and 25µm ThermoTape films have a 4x difference in TSP content, they contain the same concentration of TSP at 1%. Thus, if only the top 0-25µm of PSA+TSP contributes to the surface TSP content during the drying step, no difference in surface concentration of films over 25µm would be visible. Another hypothesis is that in a thinner film there is less of a kinetic barrier for the TSP to make it to the surface, as shown in Suk, et al., [82]. Suk demonstrated that they saw an increase in surface modifying macromolecule migration to the surface with a decrease in film thickness [82]. Another hypothesis for why 25µm yielded a larger TSP surface concentration is given the thinner PSA film, the TSP may be more influenced by the surface energy of the PET film. Future experiments will be conducted to further characterize the sub surface TSP gradient and the TSP surface migration mechanism. One experiment could involve coating thinner ThermoTape films, such as 10, 15, and 20µm, to test if these films lead to a decreased TSP surface concentration after drying. If a 10µm ThermoTape shows a decrease in surface concentration, and 15 and 20µm films have similar concentrations to the 25-100µm films, this could indicate that the surface TSP on a dried film came from 10-15µm beneath the surface. We will conduct surface energy measurements of pure PSA, PET, and TSP, take more AFM images with improved quality and scales, and use X-ray photoelectron spectroscopy to characterize the subsurface. We also will fabricate and characterize different PSA thicknesses with different TSP concentrations.

5.5.2 First pilot study

The first pilot study provided promising results that the temperature sensitive mechanism does not hinder long-term wearability. The base PSA for ThermoTape, AH-115, is described by Henkel as a long-term wear adhesive, with wear times demonstrated up to 18 days on a polyurethane backing [57]. This means that the risk for ThermoTape succeeding as a long-term wear tape does not come from the PSA, but instead the surface TSP nanodomains. Prior to this study, I hypothesized there was a chance that surface TSP could decrease the long-term capabilities, with the non-adhesive surface nanodomains potentially acting as initiation sites for early adhesive failure. This proved to not be the case, as ThermoTape samples exhibited reasonable wear over a 7-day period when compared to Tegaderm™. While ThermoTape has higher adhesion in vitro, as shown in comparative peel testing from Fig. 5.2, it did have slightly more wear than Tegaderm™. Tegaderm™ had a wear of 5.5, and 100µm and 50µm ThermoTape had wear values of 5.25 and 4.5, respectively. Despite the higher peel force than Tegaderm™, ThermoTape wear was likely less than Tegaderm™ not due to MVTR, but because of the stretchability of the Tegaderm™ polyurethane backing in comparison with the 4.5µm PET ThermoTape backing. While the MVTR is likely acceptable based on the discussed Henkel MVTR data in Table 4.2 and Section 4.1.1.2, PET lacks the ability to flex with the skin at the site of application, while polyurethane is exceptionally flexible in all directions, with a reported elongation of 400-500% when tested with the ASTM D-412 method for the ArgoMedPLUS® 18411 film [54]. This enables polyurethane to flex with the skin [83]. Regular motions in daily life can cause skin strains of up to 40%. These strains must be sustained by the backing to avoid stress on the skin-adhesive interface [84-88]. PET is unable to flex with the skin, so as the skin flexes against the PSA-skin interface, and the

PSA is attached to a non-flexible backing, a shear force is created at the PSA-skin interface. These repeated shear force stresses can increase wear over time. These results are positive, as they indicate that ThermoTape is suitable for long-term wear. We expect that when ThermoTape is fabricated with a polyurethane backing that is stretchable, it will have superior wear to Tegaderm™, due to the higher in vitro peel testing results (Fig 5.2) and Henkel data with AH-115 demonstrating 18-day wear on polyurethane [57].

Pain results from this study are positive, with both 50µm and 100µm ThermoTape exhibiting less pain than Tegaderm™, with pain values 42% and 28% less than Tegaderm™, respectively, as shown in Table 5.5. In vitro peel testing data from Table 5.5 shows that KRT had a peel force value 48% less than Tegaderm™. This is similar to the 42% difference between 50µm ThermoTape and Tegaderm™ on skin, indicating that 50µm ThermoTape removal from was likely similar to a low adhesion tape like KRT.

5.5.3 Second pilot study

The second pilot study was done to refine the heat pack application time for 100µm ThermoTape and to test the Cardinal Health Instant Hot Pack for the first time on skin. This is the heat pack used at HMC, and with an upcoming study at HMC, we had to understand if their heat packs were compatible with ThermoTape. 100µm ThermoTape was removed after 24 hours of wear and after Dynarex heat pack application for 30, 45, and 60 seconds. Pain decreased with application time, decreasing 28% from 30 to 60 seconds. This shows that more time was needed to penetrate the thicker PSA layer compared to the 50µm ThermoTape, which has been optimized for 30 seconds of Dynarex heat pack application.

On the other arm, 50µm and 100µm ThermoTape were removed with the Cardinal Health heat pack, which was applied for 30 seconds prior to removal. 50µm and 100µm ThermoTape removed with the Cardinal Health heat pack had much higher pain values than tape removed with the Dynarex heat pack on the other arm. 100µm ThermoTape removed with the Cardinal Health heat pack for 30 seconds had a pain value of 4, while 100µm ThermoTape removed with a Dynarex heat pack had a pain score of 2.25, a 44% difference. 50µm ThermoTape removed with the Cardinal Health heat pack also had a high average pain value of 3.62, which is 107% higher than the pain reported in the second clinical study where a Dynarex heat pack was used for 30 seconds on 50µm ThermoTape. This shows that 30 seconds of the Cardinal Health heat pack is not long enough for ThermoTape removal, and that Cardinal Health heat packs may need to be applied longer to initiate the temperature sensitive response, which was tested in the third clinical study.

5.5.4 Third pilot study

The third pilot study was done to investigate the effect of a paper towel thermal barrier on ThermoTape removal with a Dynarex heat pack and to test the Cardinal Health heat packs with longer application times. In our recent customer discovery work, we asked nurses if they would use a thermal barrier when using ThermoTape. Many nurses indicated that they would use a paper towel as a thermal barrier. Additionally, our HMC partners suggested that we use a thermal barrier for the upcoming HMC study to keep patients comfortable, as we may be testing on older patients. The previous pilot test was the first we tested on subjects over 60, and these subjects reported that the heat pack was too hot. We learned from the HMC team that this is more likely to occur in older patients due

to a thinner dermis and decreased blood flow [89]. As such, the HMC team suggested that we use their heat pack (cooler than Dynarex, as shown in Fig. 4.3) or our heat pack with a thermal barrier.

During this study, subjects reported that the Dynarex heat pack with the thermal barrier was pleasant and comfortable, and that it was not close to the pain threshold. This contrasts with previous tests, where some subjects were fine, some indicated that it was bearable, and a few asked for a thermal barrier. Pain reduced with the amount of time the Dynarex heat pack was applied to the skin and reduced significantly at 60 seconds. While only 5 subjects were tested, this pain value is lower at all three application times than we have seen in previous testing where ThermoTape was removed with heat. For example, the average reported pain in this study for ThermoTape when removed with a Dynarex heat pack applied for 60 seconds with a thermal barrier was 0.50, while the 53-person clinical trial yielded an average pain value of 1.15. This was when Dynarex was applied for 30 seconds without a thermal barrier, which had been optimized. Subjects can have different relative pain values from study to study if the sample size is low. However, these lower than usual pain values could be due to having a skin temperature right below the skin pain threshold. The skin pain threshold is 45ºC, and skin temperature over this is likely to induce a pain response, which could have contributed to higher reported pain values from tape removal in our other studies when a thermal barrier is not used. While the Dynarex heat pack with a thermal barrier was much cooler on skin as reported by subjects, infrared data shows that skin was heated to the ideal temperature. Calibration data was positive, with results within 1ºC from the expected with small standard deviation values. Skin warmed with a Dynarex heat pack for 60 seconds with a thermal barrier

yielded a skin temperature of 44.4ºC, which is right below the skin pain threshold, and yielded record low ThermoTape pain values upon removal. This suggests that applying a Dynarex heat pack for 60 seconds with a paper towel is the best option for the HMC study. Use of a thermal barrier prevented crossing the skin pain threshold, while also providing sufficient warming for the tape. By keeping the skin temperature below 45ºC, it is possible that reported pain from removal will be less than if the skin pain threshold was passed. This will be further investigated, with the FLIR thermal camera used to characterize skin temperature with Dynarex heat packs applied for 30 seconds without a thermal barrier to investigate if the skin temperature reached over 45ºC in our previous studies, which it likely did if it reached 44.4ºC with a thermal barrier.

Applying the Cardinal Health Instant Hot Pack for 60 seconds without a thermal barrier did not heat the skin sufficiently to activate the temperature-sensitive release in comparison to the Dynarex heat packs in this study. This is seen by the infrared data, which shows a skin temperature of 40.3ºC, associated with a pain rating of 1.8, which is higher than the Dynarex data. However, 1.8 is a 50% decrease in pain from when the Cardinal Health heat pack was applied for 30 seconds in the second pilot study (Fig. 5.8). This shows that 60 seconds did reduce pain more than 30 seconds did, but not to the degree that the Dynarex heat packs did.

This work refined our current heat pack approach for the upcoming HMC pilot test, where we will use Dynarex heat packs applied for 60 seconds with a paper towel thermal barrier.

5.5.5 Future Harborview Medical Center pilot testing

5.5.5.1 Motivation

As stated on our IRB application, the purpose of this study is to determine the effectiveness of ThermoTape in a pragmatic clinical care setting under controlled conditions. Previous pilot studies have helped define the protocol for this upcoming pilot study. Proving ThermoTape effectiveness for long-term wear against an industry standard tape at a hospital will act as an inflection point for future ThermoTape development. This study will give insight into the heat pack workflow in a hospital setting, how patients respond to heat, how ThermoTape performs in a hospital environment from a wear and pain perspective, and if ThermoTape results in less pain than Tegaderm™ with similar wear. Positive data from the clinical study will lead to a larger clinical study at HMC once manufactured samples are created, as outlined in Chapter 6. The protocol for this proposed pilot study is currently pending IRB approval. The tape for the pilot study has been fabricated and characterized, the students have access to HMC, and we have the necessary supplies and training. Once IRB approval is granted, the study will start the following week.

5.5.5.2 Study design

The inclusion criteria include 18+, have been admitted to HMC, have an orthopedic injury, have an anticipated 2+ day length of stay, and have accessible skin in one upper extremity. The exclusion criteria include bilateral upper extremity injuries requiring splints, any abnormal skin conditions – chronic or acute (burns, road rash, eczema etc.), if the subject is unable to consent, and if the subject does not speak English.

For recruiting, admission lists will be screened for patients with injuries likely to require a 2 day or more length of stay. Patients will be recruited in person by the study coordinator

who will talk directly with the patients in their patient room at a time when the patient seems comfortable and is not receiving active medical care. Patients will have the information as laid out in the consent form reviewed with them. They will be told this is an optional activity that can be stopped at any time, and that we are testing new forms of tape and would like to try two versions on their upper extremity as well as a standard adhesive. They do not have to actively do anything. Study subjects will receive $20 a day paid by check from the University up to $120 – partial days will receive the full $20.

3 pieces of tape will be placed on the upper lateral arm “similar to where vaccinations are given” and above where blood pressure cuffs are applied. This includes 50µm and 100µm ThermoTape and Tegaderm™ in 1x2 inch samples. The patient will be visited each day they are in the hospital to address any concerns and to ensure that the tape is still adherent. Any loose tape will be removed. On the scheduled date of discharge the tapes will be removed and a patient survey administered to document the amount of pain involved in the tape removal if any. Pain will be self-reported with the pain scale from our previous study, shown in Fig. 4.7. Both ThermoTape samples will be removed with Dynarex heat. This heat pack will be activated by shaking it for 60 seconds, applying a paper towel as a thermal barrier over the tape and between the patient and heat pack, and applied for 60 seconds before removal.

5.5.5.3 Expected outcomes

The expected outcomes are that both 50µm and 100µm ThermoTape will be less painful to remove than Tegaderm™, and that both thicknesses will show similar wear to Tegaderm™. The peel test data in Fig. 5.2 shows that both the 50µm and 100µm ThermoTape have a higher peel force than Tegaderm™. This indicates higher holding

power, and thus potentially lower wear. However, given the discussed limitations that Tegaderm™ is made with stretchable, high MVTR polyurethane, which is designed for long-term wear, while we are using a 4.5µm PET backing that is not as stretchable and has a lower MVTR, we may see slightly more wear than Tegaderm™. As a pilot study, the sample size is low with just 10 patients, so results likely will not be statistically significant. Tape will be removed by ThermoTape team members instead of a nurse. ThermoTape will not be sterilized, which can lower the adhesion levels. Future testing will involve a larger population, sterilized ThermoTape with a polyurethane backing, and removal by nurses. This study will potentially show that ThermoTape resulted in less pain than Tegaderm™ when removed with a heat pack, and it will give insight into the heat pack workflow in a hospital setting, how patients respond to heat, and how ThermoTape performs in a hospital environment from a wear and pain perspective.

Chapter 6: Manufacturing development

Interviews during the I-Corps™ provided a clear understanding of the stakeholders in the medical tape commercialization process, especially the manufacturing process. To scale up manufacturing outside of the lab, we learned that we would work with a coater (a contract manufacturer for adhesive coating) who will coat rolls of ThermoTape, which is then sent to a converter, who die cuts the rolls, introduces a liner system that allows for easy tape application, packages the product, and ships the product to a sterilizer. The sterilizer will sterilize the product, and then ship to a ThermoTape warehouse, likely hosted by a company like Shopify. To sell to hospitals, we will bring the completed product back to our first target hospital with our existing product champions to introduce to the Value Analysis Committee. As a result of this I-Corps™ program, many of the stakeholders in this process have been selected and working relationships have begun. This process will be elaborated in this section and is illustrated in Fig. 6.1 below. The motivation for these next steps is to demonstrate to future partners and investors that ThermoTape can be manufactured with high volume methods, is compliant with regulatory requirements, and that this compliant manufactured tape outperforms industry standard tape in a hospital environment.

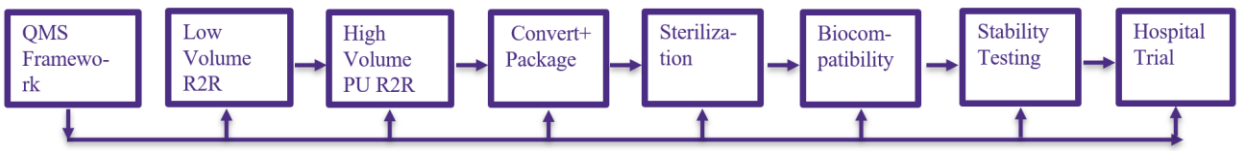


Fig. 6.1: ThermoTape manufacturing development process

6.1. Quality management system development

Working with our QMS consultant, we will initiate the ThermoTape QMS and the design history file (DHF). Our consultant will work with our team to train the whole team, including the students, to remain compliant during future product development activities. We will initiate a QMS that has appropriate procedures for our business maturity, including design procedures, supplier selection and management, and training. Although ThermoTape is a Class I 510(k) exempt medical device that only requires FDA registration, a QMS and a DHF developed under this QMS are still required. The following activities in this chapter that are within the QMS regulation scope will be completed under the QMS system.

6.2. Temperature sensitive polymer scale-up

The TSP we have used for the past few years was made in a UW polymer chemistry lab. However, these are small scale batches on the order of 20 grams. A commercial ThermoTape product must use TSP synthesized by a chemical company with adequate quality control systems under FDA medical device regulations. National Polymer (Chagrin Falls, OH) will produce 200 grams for pilot roll-to-roll (R2R) fabrication of ThermoTape. This initial lot of TSP will be characterized with differential scanning calorimetry (DSC), gel permeation chromatography (GPC), and Nuclear Magnetic Resonance (NMR). We will compare this data to data from our UW baseline TSP batches. If the data is acceptable, we will fabricate lab scale samples of ThermoTape for peel force testing and atomic force microscopy (AFM) imaging to verify that the TSP from National Polymer yields a similar response to our lab-scale TSP- a 70% or more reduction in peel force when warmed from 25ºC to 45ºC. This will be followed by a small pilot study with 5-10

subjects to verify in vivo. This will be done by placing two pieces of ThermoTape on one arm. 24 hours after application, one piece will be removed with a heat pack, and the other without a heat pack. This will follow a similar procedure as outlined in prior clinical testing above, with a requirement of a 60% reduction in pain. The quantifiable outcomes include DSC, GPC, and NMR data from National Polymer TSP, and AFM, peel testing data, and pilot study data of National Polymer ThermoTape prototypes. The technical outcome will show that larger scale TSP production is feasible and high quality.

6.3. Roll-to-roll manufacturing

6.3.1. Introduction

The standard commercial manufacturing process for acrylic medical adhesive tapes consists of coating the solvent-based adhesive material onto a backing substrate, removal of the solvents, solidification of the viscoelastic adhesive and converting the final material into customer-specific shapes and sizes. This is done using a roll-to-roll process (R2R), which is how newspapers or flexible solar cells are made. An R2R system begins with a roll of backing, which may be on a carrier if it lacks sufficient mechanical properties to be pulled through the system. This is unwound and coated with a layer of adhesive. This coated backing then travels through a series of ovens at a specific speed, which removes solvent. The line speed and oven temperatures and air flow depends on the specific adhesive being coated, meaning the process must be optimized for every new PSA.

6.3.2. ThermoTape considerations

Usually, in modern R2R drying processes, solvents are removed in-line with forced convection of heated air. A variety of defects can arise in the drying process. Blistering

and pinholes due to rapid solvent evaporation are the most frequent defects in the manufacturing of adhesive tapes. Since the solvent content of our adhesive material is high (56%) and the coated liquid film is moderately thick, the solvent removal will be the controlling factor for the speed of the overall R2R process [55]. The temperature and airflow must be optimized in separate zones along with the line speed. Our lab oven prototype drying conditions of 120ºC for 10 minutes serves as a starting point for temperature and airflow. The most useful lab data were the benchmarks of the TSP nanodomain size and surface area density (characterized with AFM) and reduction in peel force with heat. After R2R coating, these lab benchmarks can be used to verify which conditions yield the best ThermoTape performance.

6.3.2.2. Double transfer

Our next goal is to fabricate ThermoTape with a transparent backing acceptable for medical use that is flexible and has very high moisture vapor transmission rates and is standard material for covering P/IV lines for long-term wear, unlike the PET that we used for our prototypes. Medical tapes do not use PET and must use PU for the high breathability and skin conformability properties. We will use the same PU backing that is used in Tegaderm™. However, PU cannot withstand the high temperatures used for PSA solvent removal (drying). Therefore, ThermoTape incorporating a PU backing must be fabricated using an intermediary substrate material, such as a temperature stable release liner. This is common practice in industry, and is called a single transfer. However, the temperature responsive additive in ThermoTape produces morphology only at the adhesive/air interface that must be preserved. Hence a two-step process, called a double transfer between release liners, is required. This double transfer process is performed in

industry but is uncommon for medical tapes. To accomplish this process, the ThermoTape adhesive is first coated on an “easy” release liner, dried in a series of R2R heating zones, and then transferred to a “tight” release liner. Finally, the tight liner and PU backing are laminated together in the R2R machine. A tight liner has a higher surface energy than the easy liner, so that applying pressure to the liner will transfer the ThermoTape adhesive from the easy to the tight side. The PU has a higher surface energy than the tight liner, so that lamination allows transfer from the tight liner to the PU. If the surface energy of these three carriers is too close together, then there can be “confusion”, which is when there is an incomplete PSA transfer during lamination. The liner surface energy will need to be optimized so that the transfer is consistent and without confusion. Additionally, the lamination force for each transfer step will need to be optimized and defined. This double transfer will allow ThermoTape fabrication on a polyurethane backing, similar to the backing of our benchmark, Tegaderm™.

6.3.3. Pilot coating at National Polymer on a pilot coater

National Polymer, the company that will make small scale batches of TSP for R2R coating, also has a pilot R2R coater. The pilot coater at National Polymer has a smaller web size (width) than found in a larger manufacturing plant. This pilot R2R system will be used to narrow down the range of the coating parameters (zone temperatures, line speed, air flow) to save costs at DermaMed, who has an industrially sized R2R coater. Using this system allows for using less material during testing and not consuming resources at a larger scale manufacturing line for the purpose of initial testing. The pilot coating is done before moving to a larger system as costs are lower during this investigational step.

We will start with the standard temperature, air flow, and speed used for the commercial base PSA in ThermoTape (Duro-Tak AH-115). The AH-115 will be mixed with the TSP, the liner system prepared in the R2R coater, and the ovens and line speed set to typical AH-115 conditions. We will coat ThermoTape with these conditions. Once it is coated, passes through the ovens, and is dry, can be rolled on itself. At this point, the oven temperatures and air flow can be adjusted, and the speed modified to create a new set of variables for coating additional uncoated sections of the release liner. The conditions will straddle the AH-115 standard conditions. Once the ovens are stable, another several additional feet of TSP/PSA can be coated and run through the R2R drying zones. This process will repeat until a roll with numerous batches with different variables is fabricated. We anticipate running ten different conditions with different combinations of zone temperature, line speed, and air flow that straddle the typical AH-115 conditions but with a large enough range of drying conditions to understand the effects of the different drying zone temperatures on the TSP size and surface concentration and peel force reduction with heat. These ten batches will be analyzed at the UW using AFM and peel testing. The quantifiable outcome is the tested R2R conditions and the associated peel testing and AFM data. This will highlight the top condition that yielded the optimal ThermoTape performance. The technical outcome is verification that ThermoTape can be successfully manufactured on an R2R system under a set of fabrication conditions that yields the desired ThermoTape performance. The coater parameters that yielded the best results will serve as a baseline for development on an industry scale R2R coater.

6.3.4. Pilot coating at DermaMed on an industrial coater

DermaMed offers a large footprint R2R coating system with high production capacity. They are a well-respected coating supplier, and their products are found in wearable medical devices, medical disposables and dressings, and on diagnostic backing cards, electrodes, biosensors, and surgical drapes. We have worked with DermaMed over the past six months to generate a series of tests that we will run on their R2R coating system. The results from our pilot line work with National Polymer will form a valuable set of starting parameters for the larger DermaMed R2R system. DermaMed will follow the same process as National Polymer to create a single roll with four different conditions. This will be completed on their industry scale coater, where they will stop production of another product for a few days to run this trial. This initial run will include samples on both PET and polyurethane. PET will enable simple peel force testing and characterization, while more flexible and compliant polyurethane will allow for clinical testing. A ThermoTape team member will be at Derma Med during this work to capture manufacturing subtleties and aid in reducing the time to run trials. When we receive samples from DermaMed, we will characterize them with methods from the previous milestone. The quantifiable outcomes are the characterization data and a selected set of variables for optimal ThermoTape performance on an industry R2R coater. The technical outcome is verification that that ThermoTape can be successfully manufactured on an industry R2R system.

6.4. Converting

6.4.1. Introduction

A converter is a company that receives rolls of tapes from coaters like DermaMed and cuts and processes the roll into a product that meets the product specifications. They can

offer a variety of services depending on the company. Typically, they will cut the adhesive into the proper shape and size, prepare a liner system for easy application, and package the product.

6.4.2. Pilot converting at Marian

Through the customer discovery process, the ThermoTape team found Marian and intends to work with them for the converting process. Rolls of ThermoTape will be sent from DermaMed to Marian, who will develop dressings and packaging that meets our specifications. Marian is a well-respected medical tape converter. We have been in contact with Marian for over a year, and have defined our product specifications, including the desired size, materials, and packaging. Marian converted ThermoTape product will look similar to Tegaderm™ film dressings, which have a “dead area” that allows for simple application without touching the adhesive. These will be packaged in sets of 10, like Tegaderm™. Converted ThermoTape samples will be shown to a group of 10-15 nurses for feedback. Nurses will be asked to apply ThermoTape to a pediatric dummy and asked for feedback on the ease of application in comparison with a similarly sized Tegaderm™ patch. The deliverable is a report that includes the converting specifications, nurse feedback, and images of the final converted ThermoTape, and the technical outcome is validation that converted ThermoTape meets the usability needs of our users.

6.5. Sterilization

6.5.1. Introduction

Tape in this trial will be sterilized before use so that it is more equivalent to a finished product. There are many methods available for sterilizing medical adhesives. Typically,

an adhesive is first created as a roll by a coater (contract manufacturer), sent to the converter who cuts the rolls into the proper shape for a final product, and then sent to the sterilizer. The sterilizer can use a variety of methods to sterilize adhesives. However, ethylene oxide has a long cycle time and there are many papers that state that this method leaves ethylene oxide residue on the tape, which could decrease performance and lead to residue. Gamma and hydrogen peroxide generate radicals with acrylic-based adhesive. These methods extract hydrogen from the backbone, which can then crosslink with nearby chains. This causes an increase in PSA shear force, which will cause the peel force to drop. As we are looking to have the maximum adhesion we can, we want to avoid a sterilization method that mitigates adhesion. We recently tested hydrogen peroxide and saw a 25% drop in peel force when compared to samples that were not sterilized. We will investigate ethylene oxide and test for residue. If residue is present, we will look to mitigate it, and use gamma and hydrogen peroxide as backups. Our advisor at Henkel said that a decrease in peel force with these typical sterilization methods is standard and accepted, but we want to maintain higher adhesion if possible. Our selected backing, ArgoMedPLUS® 18411, withstands ethylene oxide and hydrogen peroxide sterilization.

6.5.2. Pilot sterilization at Steritech

Marian will send converted and packaged ThermoTape to our sterilizer, Steritech. ThermoTape will undergo a series of sterilization tests with ethylene oxide, where boxes of ThermoTape will be sterilized for varying amounts of time. Sterility will be verified by Steritech to show that the samples meet sterilization requirements. Sterilized ThermoTape will be characterized with peel testing by the team to verify that sterilization

does not affect the temperature-sensitive features of ThermoTape or result in significantly lower peel force at room temperature. The deliverable is a report that includes the sterility conditions and testing data, the top sterility conditions, and peel testing data. The technical outcome is that sterilization does not negatively affect ThermoTape performance and defined sterility conditions.

6.6. ISO 10993-1:2018 -biological evaluation

6.6.1. Introduction

After sterilization, if funding allows, we will complete ISO 10993-1:2018 - Biological evaluation of medical devices testing before the trial. This testing will most likely be done through NAMSA, who has provided a quote for the tests required for this standard. These tests include cytotoxicity, skin irritation, and skin sensitization. Our lab synthesized TSP passing this standard is a low-risk, but critical aspect of this moving to the clinical trial. The TSP is a wax like inert copolymer, and we do not expect any biocompatibility issues.

6.6.2. Evaluation at NAMSA

Samples will be sent from the sterilization supplier to NAMSA, who will complete ISO 10993-1:2018 -biological evaluation, an industry standard and FDA required test. These tests include cytotoxicity, skin irritation, and skin sensitization. The TSP passing this standard is a low risk but critical aspect of this moving to the clinical trial. Every component of ThermoTape, including the PSA, backing, and liner, has already demonstrated ISO 10993 compliance. The purpose of this test is to show that the addition of 1% TSP does not lead to cytotoxicity, skin irritation, and skin sensitization. Materials like the TSP are routinely used in cosmetic formulations. TSP is a wax-like inert copolymer, and we do not

expect any biocompatibility issues. The deliverable is a report that will be provided by NAMSA with the testing data and analysis. The technical outcome is that the addition of the TSP does not lead to any cytotoxicity, skin irritation, and skin sensitization. This data has been indicated as crucial for partners to want to work with us.

6.7. Product stability testing

6.7.1. Introduction

Adhesives undergo stability testing to demonstrate that the product has sufficient shelf life, is moisture resistant, and to develop the storage temperature range. As we are using an existing and well testing adhesive, our stability testing will focus on what is unique to ThermoTape: temperature stability.

6.7.2. Study design

Converted, packaged, and sterilized ThermoTape will undergo stability testing. Initial data with lab-scale prototypes have indicated stability, but this manufactured product will undergo more rigorous testing. Samples will be aged at 40ºC for extended time periods and will be analyzed using AFM and peel testing. The deliverable is a report that will outline the characterization results and recommended shelf life and storage conditions. The technical outcome is an understanding of the stability of ThermoTape temperature sensitivity. This will highlight if the TSP surface nanodomains are stable for long periods of time at different temperatures.

6.8. Alternative manufacturing strategies

In the case that the outlined R2R process is not compatible with ThermoTape, there are several alternative manufacturing strategies which have been outlined in our published

patent application [91]. There is a risk that drying occurs too quickly for TSP migration through the PSA to the surface. While unexpected, the approached below offer possible alternative approaches.

One method is a spray coating approach. The additive is dissolved in a carrier solvent such as hexane, and droplets are dispensed through an inkjet nozzle. Following this surface deposition, the excess solvent is removed by evaporation, causing possible surface nanodomain formation. This evaporation step would be done before drying as polyurethane backings are not heat resistant. This method would reduce the amount of TSP used, as pure PSA could be coated without TSP. This could save costs, but coaters have indicated that they currently lack the infrastructure for spray coating on an R2R line, although it is feasible. This indicates increased upfront costs, as well as increased technical risk with this approach.

Another alternative method involves coating pure PSA and then coating a thin film of either PSA and TSP at a high concentration, or TSP dissolved in a solvent like hexane. As we hypothesized in Section 5.5.1 that we are mostly interested in near surface TSP, this method would enable less TSP usage. The system would then be run through the R2R ovens, drying out the PSA and the TSP film, potentially leading to the desired surface morphology. This approach would be compatible with current R2R systems. This method can be further differentiated by a combination of grooving or embossing the first PSA surface, and adding the additional layer of PSA with the TSP that is then coated over the first PSA layer.

TSP could be added directly onto a coated pure PSA film. Patterning the TSP directly on to the adhesive could be achieved by a printing process such as flexography, inkjet

printing, offset printing, gravure, electrohydrodynamic printing, or screen printing. This could be done in roll or sheet formats. Other non-contact printing techniques such as inkjet, aerosol jet or electric field assisted jet printing could also be used to apply the TSP onto the pure PSA layer. It may also be possible to transfer the additive to the adhesive surface by laser ablation printing in which laser energy, which can be delivered in a controlled pattern, is used to ablate or thermally assist transfer of additive from a carrier film in contact or in near proximity to the adhesive surface.

6.8.1. IP protection and future opportunities

The ThemoTape IP portfolio is based on formulating a temperature-responsive adhesive that can be safely removed with the application of heat while on human skin. The UW CoMotion group manages the IP. Currently, a non-Provisional PCT Patent application #63/075,946 was Filed 9/9/21, "Pressure sensitive adhesives and related methods", UW File # 48992, and 49166 for small molecule temp-sensitive additives to PSA. Two provisional patents were combined and converted, which is now published after over 3 months of extensive preparation by CoMotion at the UW. This high-quality patent protection was prepared with the expectation of divisional patents to be created by USPTO actions soon. The UW owns the IP, and the ThermoTape team will license this IP when they spinout from the UW.

Chapter 7: Conclusion and future work

7.1. Translational efforts

7.1.1. Regulatory Strategy

With the assistance of our regulatory consultant David Hammond, we previously submitted an FDA Pre-Submission. The FDA stated that we can heat the skin up to 45ºC, and that with our previous near infrared (NIR) wand design, we would be a Class 1 510(k). This early Pre-Submission provided key guidance on a product requirement of having a transition temperature below 45ºC. While the NIR wand would be a Class 1 510(k) device, medical tapes and heat packs are regulated as Class 1 510(k) exempt medical devices. Dave Hammond believes that based on previous products in this space and our simplified approach for thermal release of using existing heat packs, it is likely that ThermoTape is Class 1 510(k) exempt. This will allow for an accelerated commercialization pathway, and an opportunity to reach sales quicker than typical medical device startups. We plan to submit another FDA Pre-Submission after the HMC study to confirm the 510(k) exempt approach.

7.1.2. Market sizing

ThermoTape could reduce medical errors, pain, anxiety, and nurses' time, which are strong drivers for new product acceptance. MARSI exists due to medical tape limitations, and ThermoTape could greatly reduce, if not eliminate, MARSI while maintaining the highest quality of care. The initial target market is hospital systems, where ThermoTape will be used to attach wound care dressings and critical medical devices to the skin, such as IV lines, nasogastric tubes, and PICC lines. This market was identified and validated during the NSF I-Corps™. Hospitals will buy ThermoTape to increase the quality of care

and save money by preventing skin injury (occurring ~20% of the time) and device dislodgement, while improving patient and caregiver satisfaction. Future opportunities will focus on expanding to general hospital systems, clinics, geriatric care facilities, and wound care. The total addressable market (TAM) is the worldwide medical adhesive tapes market, estimated at $9.4B USD (2022) and growing at 5.9% CAGR [92-94]. We expect ThermoTape to eventually be a global product like Tegaderm™, as the need is large and prevalent worldwide. The serviceable addressable market (SAM) is $1.88B, which is the percentage of the population that is at risk of MARSI and device dislodgement. We do not expect ThermoTape to be used on every patient, as 80-90% of patients do not experience MARSI. From a device dislodgment perspective, patients that know why these devices are on them are less of a risk- pediatrics or patients that may be confused are more likely to experience device dislodgment. Given the extra step of warming ThermoTape prior to removal and the slight increase in cost, ThermoTape should be used mostly on at risk patients. MARSI prevalence in the general population is 13%, and the mean rate of IV-line dislodgement is 17.5% [6, 7, 14]. A portion of this population overlaps, so a conservative estimate is that 20% of patients would require ThermoTape to reduce MARSI and device dislodgement. To initially address SAM, we intend to first target all hospital systems in North America before expanding to clinics, long-term care facilities, sports/physical therapy, and direct-to- consumer. North America accounts for 47% of the TAM for $4.4B, and 44% of that market is hospital systems, or $1.94B [93,]. If ThermoTape should be used on 20% of patients in hospitals in North America (pediatrics and geriatrics, as supported by NSF I-Corps™ customer discovery

interviews), and we capture 30% of these hospitals, the serviceable obtainable market (SOM) would be $116M. The breakdown of TAM/SAM/SOM is shown in Fig. 7.1.

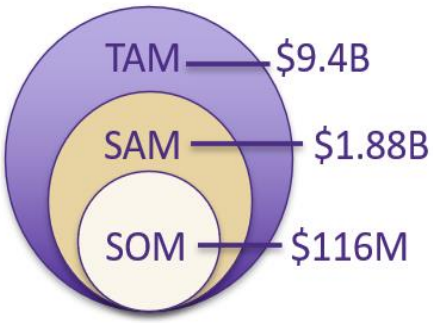


Fig. 7.1: Market Sizing. TAM: worldwide medical adhesive tapes market in 2022. SAM: The percentage of the population that is at risk of MARSI and device dislodgement. SOM: Patients at risk of MARSI in 30% of US hospitals.

The market that ThermoTape captures will grow as ThermoTape enters more hospitals, expands outside of hospital systems, and expands worldwide. Additionally, ThermoTape can expand to numerous other product lines. Our first product is a small (2.375 inches x 2.75 inches) adhesive patch like Tegaderm™, used to adhere critical medical devices to the skin. Our first pipeline product will be a larger adhesive patch (4 inches x 4.75 inches) for wound care. These analogous Tegaderm™ products are shown in Fig. 7.2.

Fig. 7.2: Small and large Tegaderm™ dressings given to the team from Dr. Kleweno from Harborview. The small patch is used for attaching IV lines and other medical devices, and the large is used for wound care dressings. ThermoTape at the end of this grant will look similar the smaller Tegaderm™ in this photo, while the larger film will be the first pipeline product for wound care.

The larger patch will enter the wound care market, which is estimated at $18B and is growing at a 5.3% CAGR [94]. This product can be manufactured with a simple change at the converter. Marian can simply convert rolls from DermaMed into larger dressings, allowing for quick and low-cost access to our pipeline market. The next pipeline product will be patches for wearable medical device attachment. These patches can be cut for specific wearable medical devices at the converter. The wearable medical device market is valued at $19.5B and is growing at a 28% CAGR [95]. Other use cases in the future include cosmetics, athletic medicine, and industrial applications.

7.1.3. Commercialization

7.1.3.1 Commercialization strategy

We understand that we cannot plan on a license to occur, and that we must be prepared to pursue a startup. After our I-Corps interviews, we feel prepared to go this route, as we now understand the complicated process of bringing a medical tape to the market, having interviewed each key player in this ecosystem. These key findings are as follows, and were achieved by interviewing many coaters, converters, PSA companies, film suppliers, and founders in this space. We learned that a TSP formulator would send our temperature sensitive polymer to the coater, Henkel will send the PSA to the coater, and SWM or other company will send the backing and liners to the coater. The coater, (DermaMed or other

company), coats the adhesive and sends a large roll to a converter, like Marian. The converter cuts the roll into specific products and packages it. The converter is who we place our orders with, with the converter then placing the order to the coater. Other medical device companies, such as 3M™, place orders with a converter when they want a specific tape product. The converter has a list of coaters that have an associated catalog of products. The converter then orders from the coater who has the best fit for the order they need to fill. The converter then sends the product to a sterilizer, and then the finished product is sent to a ThermoTape warehouse, which would likely be hosted by Shopify, as many other medical device founders we interviewed used this service. In the early stages, orders from hospitals would go directly to ThermoTape, and would be sent from the ThermoTape warehouse to the hospital. However, once we demonstrate repeat sales, we can be placed on a distribution list, at which point the distributor would order from ThermoTape and deliver the orders to the hospital. Before work with a distributor begins, sales would be generated by attending conferences, trade shows, and hiring a small sales team to directly reach out to nurses and physicians who could recommend the product to a value analysis committee at their hospital.

During the NSF I-Corps™ Program, the team interviewed members of the Value Analysis Committee (VAC) at SCH to understand the process for gaining product acceptance in a hospital system. We were told that a nurse practitioner or doctor brings a product to the VAC, and the VAC performs a clinical and economic analysis. After clinical testing and health economic analysis, the committee votes on if they should accept the product. The interviewee was optimistic for the ThermoTape health economic evaluation, given the cost saving from the reduction of MARSI and device dislodgement. Prior to this analysis,

we will have completed a clinical trial at SCH with our SCH collaborators and published the findings, so the clinical analysis during the VAC process should be successful. Because of this and our product champions at SCH, we believe that we can gain ThermoTape adoption. During the I-Corps™ interviews we learned that the first hospital acceptance is the most difficult to win - once one hospital system approves a product, others can follow more quickly by using the data from the early adopter. Next, we will expand utilization to HMC and other UW hospitals. We will plan a formal launch to increase awareness and demand generation through various sales & marketing tactics, including case studies, marketing campaigns, publications, testimonials, and conferences and tradeshows.

Securing several hospitals as customers with repeat sales will provide credibility and traction to engage with a larger distributor. Once the distributor takes over, they can take care of the promotion of the product if they see the financial opportunity, for which they would take a larger cut. Alternatively, they would just list the product in their catalog, making it easier to fulfill orders as some hospitals will use this to bypass the value analysis committee. With this route, sales would still be generated with the methods above. These findings are key outcomes from many I-Corps™ interviews, as this kind of knowledge would be difficult to acquire without a widespread net of interviews.

7.1.3.2 Future funding

Overall, the ThermoTape team will continue to pursue non-dilutive funding by submitting SBIR applications, while will pursue seed round investment of the UW spinout company and licensing options. The team received a three-year NSF PFI grant in April 2023 that funds salaries and fundamental research to determine the interaction of the TSP additive

and the bulk PSA material. Future funding will continue to build on NSF success with at least one Phase I NSF SBIR application. The probability of a successful ThermoTape NSF SBIR is increased due to the completion of the NSF I-Corps™ program and the current PFI award. NSF program managers have indicated that completion of the I-Corps™ increases the odds of a successful NSF SBIR, as the reviewers consider the business model and need as de-risked, as it was validated with 100+ customer discovery interviews. Research during the PFI award also increases the odds of a successful application, as it will provide a deep scientific basis for the future NSF SBIR application.

When the time is right, the team will pursue a seed round. The team will begin with creating a data room that has all the necessary due diligence materials. The team will pitch at the Seattle Angel Conference, SWAN Venture Fund, Pack Ventures, the Dub Pitch, Alliance of Angels, and Apis Health Angels. These are all located in Seattle. Funds from this seed round will be used to expand the quality system, manufacturing, and evaluation of manufactured ThermoTape, and for a clinical trial at SCH, register with the FDA, and initiate sales.

7.1.4. Licensing

Based on findings from the I-Corps interviews with coaters, converters, sterilizers, PSA companies, and similar startup company founders, the team believes that a license is the best option for commercialization. We believe our technology has greater value to an established company with direct customer connections, as sales could occur quicker and broader. As a high volume, low margin product, competing with large adhesive companies would be difficult. Given that costs are higher with lower volume manufacturing, it is likely the team would sell at a loss in the early stages of commercialization, in order to stay

competitive and capture early sales. This loss would need to be subsidized by fundraising. As sales expanded, manufacturing volume could increase, product margins would turn positive, and ThermoTape would be a profitable startup. The road to profitability would be risky and would require at least a series A fundraising round for sales, likely a Series B as well. The further a startup progresses down this route, the higher risk there is a failure. While this route is certainly possible and can be approached with specialty products as outlined in the next section, it is obviously higher risk than a license, which typically occurs earlier. While the financial return is not as large, the interest in the team is to get this technology out there to improve patient quality of care by reducing MARSI and device dislodgement events. Therefore, we may find it more advantageous to license ThermoTape to a PSA coating or converter company. Coating companies buy raw materials (PSAs, film substrates, release liners etc.) from many suppliers like Henkel and fabricate large rolls of inventory for selected markets. Converters purchase these rolls and fabricate specified shapes for the end-customers. Alternatively, there are PSA vertical manufacturing companies that could license such as 3M™, J&J and Avery Dennison, who have a large footprint in the adhesives space and sell directly to consumers and hospitals.

7.1.5. Micromend case

Dr. Ronald Berenson, MD, CEO KitoTech Medical Inc., Seattle, WA. Dr. Berenson leads a medical tape startup. He and Paul Leung, PE, VP of Operations, have been great mentors during ThermoTape development. They created a novel wound care technology that can close small wounds and reduce scarring. This is done with a series of microneedles that pull the wound together during healing [96]. They have sold their device

on Amazon and reached significant sales. They recently expanded to retail, selling at places like Walgreens in small packs of their specialty wound closure adhesive device. This was a novel use case of their technology to create a specialty product, allowing them to sell at higher margins given the application and the market. A similar case could exist for ThermoTape. ThermoTape could be sold direct to consumer as a similar product to what would be used in hospitals. The team continues to explore this alternative commercialization option.

7.2. Murdock funding under review

The Murdock grant application was a large part of the last 6 months of my PhD. This was a competitive grant application. A successful pre-proposal and pitch and interview led to the University of Washington nominating ThermoTape as the sole applicant this cycle. The objective and expected outcome of this grant is verifying that manufactured, converted, packaged, sterilized, and biocompatibility ISO compliant ThermoTape outperforms Tegaderm™ in a Level 1 trauma hospital. While I had defined what this looks like from the I-Corps™, I had to understand every detail in the process to write the grant. As outlined in Chapter 6, I explored the details associated with every step in the manufacturing process. If funded, the success of this grant will be measured with data that shows that a commercial ready ThermoTape demonstrates less wear than Tegaderm™ over the 10–14-day period and causes less pain and injury upon removal when compared with Tegaderm™. This positive data will represent a major inflection point in the development of ThermoTape. De-risking ThermoTape by having a clinically proven commercially manufactured product ensures the future of ThermoTape: establishing

partnerships with larger risk-averse companies, gaining investment, registering with the FDA, and capturing product sales.

7.3. Large extended wear study on the general population

7.3.1 Motivation

The team has prepared for an extended wear study at the University of Washington. We expect a minimum of 50 subjects aged 18 – 50. This will be done with manufactured tape on a polyurethane backing that has been converted, packaged, and sterilized, as outlined in Chapter 6. This will occur prior to the larger HMC study to demonstrate that the manufactured ThermoTape functions as expected in vivo before testing on hospital patients of all ages over 18. Prior to this large study, 2-3 pilot tests will be conducted to gather initial data to give confidence that this larger study will be successful with new, manufactured tape. Positive data from this large study, in combination with pilot study data from HMC will give confidence to the team and IRB to proceed with a larger HMC study.

7.3.2 Study Design

This is a 7-day study to look at the performance of manufactured ThermoTape as a long wear tape in comparison to Tegaderm™. Tape application is Day 0, and tape removal is Day 7. ThermoTape and Tegaderm™ will be applied to patients' forearms, with Tegaderm™ as a control. Subjects will send pictures of their forearms to the researchers on Days 1, 3, and 5. ThermoTape will be removed with heat, and Tegaderm™ without heat to only test clinically relevant conditions. Pain will be reported and collected. Quantifiable outcomes: comparing ThermoTape and Tegaderm™ wear performance,

injury to the skin (redness from the chromameter measurements, and TEWL from the TEWL probe), irritation during wear, and pain during removal.

The subject must meet the following exclusion criteria to sign up:

Exclusion criteria

- Subjects with cutaneous anomalies on arms that interfere with grading/measuring of test site: sunburns, infections, scars, moles, etc.
- Subjects with history of eczema, adverse reactions to adhesives or recent history of dermatitis or skin reactions
- Subjects with allergies to cosmetic products and/or plasters

Subjects must also be over 18 years old. Consent will be obtained from the subject after they enter the building. This will be done by providing the subject with a paper providing the necessary details of the trial. A researcher will be available to answer any questions that the subject may have. If consent is obtained, the subject will sign the paper and will be allowed into the room for tape application.

Following the pre-tape application preparations, ThermoTape (1 by 2 inches), will be applied horizontally, in vertical succession on the forearm. After each application, a finger will be used to rub the tapes in a vertical motion to ensure that the tape, especially edges, are fully adhered. The first area of tape application will be 2 inches distal the wrist, the second 2 inches distal the closest edge of the first piece of tape, and the third piece 2 inches distal the closest edge of the second piece. To eliminate variability, the positions

of the tapes will be randomized from subject to subject, however three tapes will always be applied on one forearm. One researcher will apply and remove all tapes.

Once all tapes are applied, subjects will not be given any limitations on their behavior or habits over the 7-day period. Subjects will then be instructed to take photos and email them to an assigned researcher on days 1, 3, and 5 after tape application. They will be shown an example photo that demonstrates how close the image should be and what lighting should be achieved. These photos will be stored on a secure Google drive, only accessible by the researchers. Reminders will be emailed to the subjects on days where they are to send photos, and the subject will reply to that email with the photo. The researcher will upload that photo to the Google drive, label it with the date and subject number, and delete the email. These photos will be used to analyze the visual condition of the tapes, including the wear and redness, which will use Tables 4.3 and 4.4.

When subjects return to have the tapes removed on Day 7, they will wait in the room for 30 minutes before any measurements take place. The wear of the tape and the redness of the skin will be recorded prior to removal. After 30 minutes, they will be given a pain survey to fill out after each piece of tape is removed, as shown in Fig. 4.7. The researcher will say: “It doesn’t have to be a whole number”. The patient will be instructed to not talk during removal unless necessary and the researcher will not talk to the subject, to eliminate possible distraction, which can reduce pain [97].

When removing the tape, an edge will be lifted and then peeled at a 180° angle at a rate of 1 inch per second. If a hair is encountered, the tape will be removed following the root of the hair to the tip. During removal, if a subject reports discomfort or the skin appears

to start tearing, removal will stop and a commercial silicon-based remover, Brava, will be used to remove the tape instead. To do so, Brava will be rubbed all over the tape and the edges, and at the crease where removal is occurring. Gloves will be used in the case Brava is used to remove the tape. Prior to heat pack activation, the corner of each sample will be lifted. A Dynarex heat pack will be activated and kneaded for one minute before application onto the subject's skin. Then the heat pack will be applied to ThermoTape for 60 seconds with a paper towel thermal barrier before removal is initiated.

Following the removal of each piece of tape, the pain survey will be collected. The skin will also be examined to see if skin stripping occurred, using Table 7.1.

Table 7.1: Skin stripping scale

Grade	Description
0	No skin stripping
1	Trace amounts, slight glazed appearance
2	Partial thickness stripping, moist, and/or wet surface
3	Full thickness stripping, extends into dermis, exudates present on test site
4	Full thickness stripping extending into dermis or in combination with extreme erythema/edema response

7.3.3. Expected outcomes

We expect that ThermoTape will exhibit less wear than Tegaderm™ over the 7-day period, while also being less painful to remove than Tegaderm™. This data will give confidence to move forward with a large clinical trial at HMC.

7.4. Future clinical testing at Harborview Medical Center

As the last milestone in the Murdock application, after the outlined manufacturing steps above are completed, we will execute a comparative single-blind clinical trial at HMC. This will build off the HMC pilot study, with an expanded number of patients, one adhesion level (PSA thickness), and manufactured ThermoTape. Dr. Conor Kleweno, Orthopedic Surgeon at HMC will be the PI for the clinical trial, as he is for the pilot test at HMC. ThermoTape that has completed a verified pilot manufacturing process, including coating, converting, packaging, biocompatibility testing, and sterilization, will be used in this trial. Manufactured ThermoTape and Tegaderm™ patches of the same size will be used in this trial. A clinical trial with Dr. Kleweno at HMC offers a unique opportunity, as his patients are often at HMC for extended periods of time. This will enable a longer clinical trial of 10-14 days, where ThermoTape and Tegaderm™ are placed on the forearm. Upon removal, ThermoTape will be removed with a heat pack, and Tegaderm™ without a heat pack. Quantifiable outcomes: Tegaderm™ and ThermoTape wear performance, injury to the skin, irritation during wear, and pain during removal. The deliverable is a submitted manuscript to a peer reviewed journal. The technical outcome is verification of manufactured ThermoTape compared to a leading medical tape at a Level 1 trauma and burn hospital.

7.5 Future Clinical testing at Seattle Children's Hospital

After testing at HMC with favorable data, the team will move towards a clinical study at Seattle Children's Hospital. Testing on ages 18+ and completing another hospital clinical test, coupled with publications in peer reviewed journals, will give confidence to move forward with testing on children. This will be done with manufactured, packaged, and sterilized ThermoTape. This study protocol will be developed with our SCH nursing team as we approach that stage of development. It will likely be a comparative test with Tegaderm™ with a real application of securing a medical device to skin. Age will be restricted to the upper range initially. Having tested successfully on patients 18+, which was done in a stepwise approach that began with 18-25 year old patients, we will likely start with patients aged 13-18, and then proceed younger with favorable data. Testing at SCH with an associated publication is a big step in the commercialization process for ThermoTape, providing critical data and validation for future value analysis committees.

7.6 Conclusion

Developing ThermoTape for my PhD has been a challenging and rewarding experience. When I joined, we used a surrogate tape from industry that had a transition temperature well above safe temperatures for skin. An NIR wand was tested for possible removal of this tape as a proof of concept. From this starting point, I completed customer discovery interviews, identified an alternative heating mechanism for release with heat packs, incorporated a compatible temperature sensitive additive with a synergistic PSA, and adjusted numerous variables to create a functional proof of concept device. I verified this proof of concept with numerous characterization methods, and then validated it in pilot studies. This led to a publication in the International Journal of Molecular Sciences. Extensive characterization of heat packs led to a proposed pilot study protocol. I transitioned ThermoTape to a 4.5µm PET backing to enable more effective human testing, while also enacting fabrication improvements to increase consistency and efficiency as we scaled and prepared for a large clinical trial. I executed a 53-person clinical trial with favorable data which led to an associated publication in the Journal of Wound Care. I validated the product through 150 customer discovery interviews and defined a commercialization model that contributed to our success with receiving grants. I created a second novel product: ThermoTape with double the thickness of PSA to provide unprecedented adhesion levels with a safe release through several fabrication trials and characterization efforts. I validated this new design in several pilot studies and prepared ThermoTape for its next steps: manufacturing and clinical testing of manufactured prototypes. ThermoTape will soon be tested at HMC, demonstrating

ThermoTape functionality in a hospital environment against industry standard tape, Tegaderm™.

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Appendix A: Clinical Trial Materials

A.1 Clinical trial recruiting flyer

A.2 Clinical trial subject application form

UnTape Clinical Trial Subject Application

* Indicates required question

1. What is your name? (first & last name) *

2. How old are you? *

Mark only one oval.

- ◯ 18
- ◯ 19
- ◯ 20
- ◯ 21
- ◯ 22
- ◯ 23
- ◯ 24
- ◯ 25

3. What gender do you identify as? If, other, please specify below. *

Check all that apply.

- ☐ Male
- ☐ Female
- ☐ Transgender Male
- ☐ Transgender Female
- ☐ Non-conforming
- ☐ Other:

4. What would be the best way to contact you? *

Mark only one oval.

- ◯ Email
- ◯ Phone Call
- ◯ Text

5. What is your email? *

_____

6. What is your phone number? *

_____

Skin Condition and Allergies

This information will not be shared. We respect the privacy of your health information. We want to ensure your safety with any skin sensitivity regarding the tape.

7. Do you have a history of the following: *

Check all that apply.

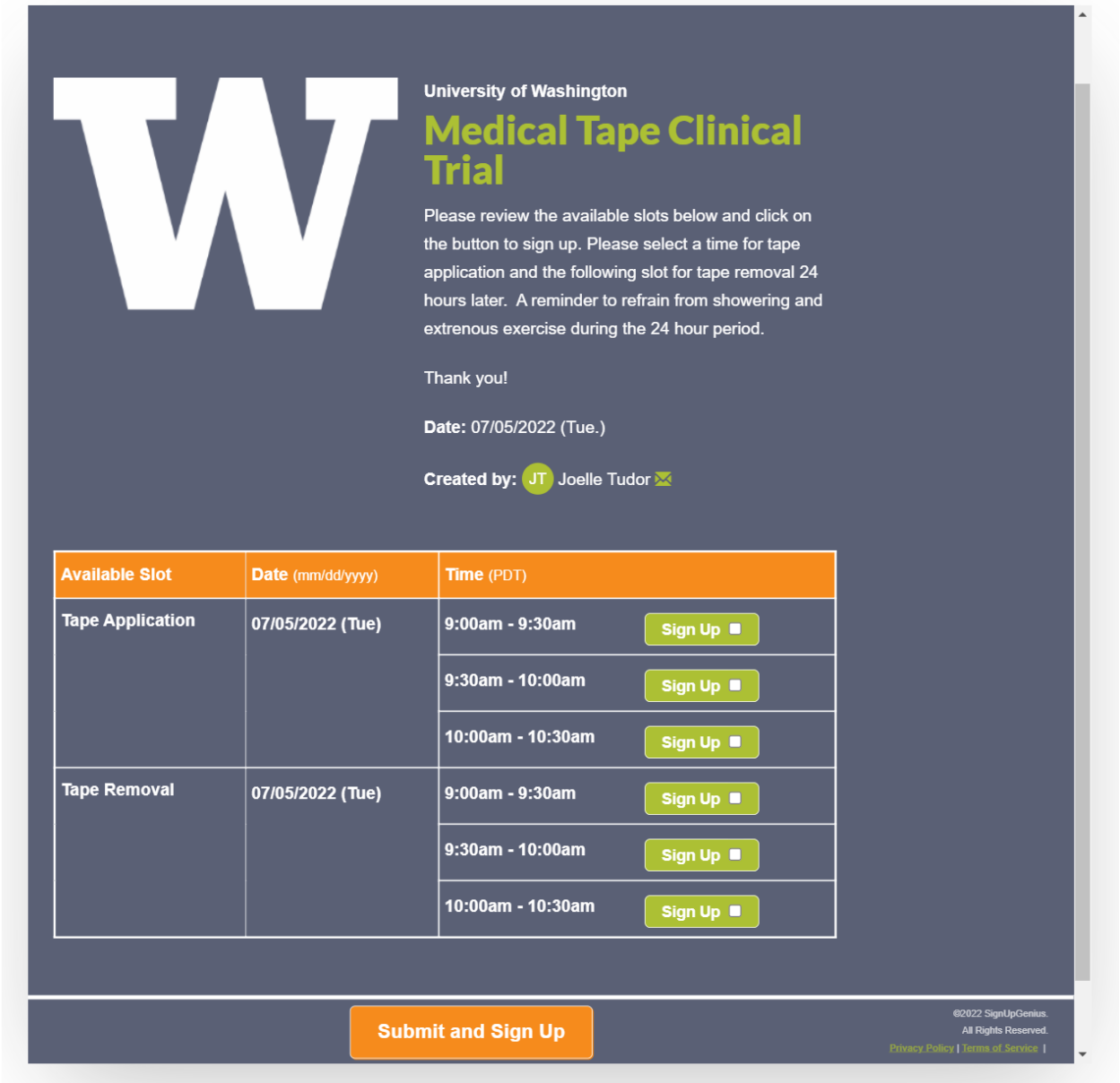
- ☐ Eczema
- ☐ Medical Adhesive Related Skin Injuries (MARSI)
- ☐ Neither

8. Are you allergic to any medical adhesives? *

Mark only one oval.

- ◯ Yes
- ◯ No
- ◯ I don't know

A.3 Clinical trial scheduling form



University of Washington

Medical Tape Clinical Trial

Please review the available slots below and click on the button to sign up. Please select a time for tape application and the following slot for tape removal 24 hours later. A reminder to refrain from showering and extrenous exercise during the 24 hour period.

Thank you!

Date: 07/05/2022 (Tue.)

Created by: JT Joelle Tudor

Available Slot	Date (mm/dd/yyyy)	Time (PDT)	
Tape Application	07/05/2022 (Tue)	9:00am - 9:30am	Sign Up
		9:30am - 10:00am	Sign Up
		10:00am - 10:30am	Sign Up
Tape Removal	07/05/2022 (Tue)	9:00am - 9:30am	Sign Up
		9:30am - 10:00am	Sign Up
		10:00am - 10:30am	Sign Up

Submit and Sign Up

A.4 Clinical trial consent form

University of Washington

Consent Form

[UnTape]

Researchers: Eric Seibel, PhD, Research Professor, University of Washington; Shawn Swanson, PhD Student, Research Assistant, University of Washington; Vivian Luu, Undergraduate Student, University of Washington; Joelle Tudor, University of Washington

We would like you to participate in a research study. This form will provide information for you to determine if you would like to be part of this study. Please read this form carefully, before deciding. Please do not hesitate to ask any questions about parts of the study that are unclear.

A description of this clinical trial will be available on http://www.clinicaltrials.gov/, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Purpose of this Study

Medical tapes are used to hold medical devices, such as an IV line, in place. The purpose of this study is to compare three different medical tapes for its safety and performance. The study will take place for 24 hours. Afterwards, the level of pain, safety, and potential effects after the tape is removed, with and without the use of a heat pack, will be monitored. The application and removal of the tape will be conducted by the research team in the lab with training from consultant and UnTape team member Ms. Ann Marie Taroc, MSN, RN, CPN.

Study Procedures

You will go to the Fluke Hall, room 104, and sit in a chair. A member of the research team will explain the procedures that has been approved by our consulting nurse. Both forearms will then be cleaned by an isopropyl wipe. The areas where the tapes are to be applied will then be inked using a skin marker. Three pieces of tape will be applied on each forearm, for a total of six tapes. An activity log will then be given to document the next 24 hours of the study.

After 24 hours, you will return to the same location as before and sit in a chair. A member of the research team will provide you with a survey to rate the pain felt from each tape removed. For one forearm, a medical grade, commercial heat pack will be applied for tape removal. After all tape has been removed, photos will be taken of both forearms. You will then wait 15 minutes to examine for any signs of skin irritation.

If social distancing guidelines disallow two people to be in the lab at a time, then the testing will be performed by you. Instructions will be provided through Zoom. Heat packs and remover

solvent will be provided, in the event this is necessary. You can stop the procedure at any time for any reason and all your data will be removed. Only your forearms will be recorded or photographed.

The application and removal process should take no more than 45 minutes. No personal questions will be asked, and you may refuse to answer any questions. You may also be asked to be removed from the study at any time, with no consequences.

Risks, Stress, or Discomfort

A low degree of risk will occur when removing tape from you. The heat pack applied is a commercial product designed for human skin use and will only be applied for a few seconds. Side effects that may occur are skin injuries, such as skin tearing, stripping, redness, irritation, or inflammation. If skin tearing or stripping occurs, an adhesive remover will be used to remove the tape from your skin. Cold packs will be available for use in case of injury. There is also a low risk of an infection occurring in the event of a skin tear. To migrate this risk, Neosporin™ and band-aids will be provided.

Benefits of the Study

There will be no direct benefits if you choose to participate in the study, however the knowledge obtained will be used to benefit society.

Source of Funding

The research team and/or the University of Washington is currently receiving funding through the WE-REACH program at the University of Washington, which acquires funding from the National Institutes of Health.

Use of Information and Specimens

The data and/or specimen obtained from you may be used in future research. We may remove any information that may identify you from the data and specimen gathered. If done, the gathered data and specimens will be provided for other researchers or studies without further permission from you. If we want to use or share data from this study, that identifies you, then a review board will decide whether further permission is required from you.

Confidentiality of Research Information

Government or university staff sometimes review studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at legal risk of harm.

We have a Certificate of Confidentiality from the federal National Institutes of Health. This helps us protect your privacy. The Certificate means that we do not have to give out

information, documents, or samples that could identify you even if we are asked to by a court of law. We will use the Certificate to resist any demands for identifying information.

We can't use the Certificate to withhold your research information if you give your written consent to give it to an insurer, employer, or other person. Also, you or a member of your family can share information about yourself or your part in this research if you wish.

There are some limits to this protection. We will voluntarily provide the information to:

- a member of the federal government who needs it in order to audit or evaluate the research;
- individuals at the institution(s) conducting the research, the funding agency, and other groups involved in the research, if they need the information to make sure the research is being done correctly;
- the federal Food and Drug Administration (FDA), if required by the FDA;
- individuals who want to conduct secondary research if allowed by federal regulations and according to your consent for future research use as described in this form;

The Certificate expires when the NIH funding for this study ends. Currently this is October 10th, 2022. Any data collected after expiration is not protected as described above. Data collected prior to expiration will continue to be protected."

Other Information

You may withdraw and/or refuse to participate in this study at any time without any consequences. Your decision to participate will not impact your academic status or any future opportunities that may occur. Being a subject in this study is not required to be a research assistant on any project.

A $50 Amazon gift card will be given to those who complete the study. Completion of the study will involve coming in for tape removal, even if no tape is left on the skin, and completion of a post-removal survey. It will be delivered 1 to 2 weeks after the subject has completes the study.

After tape removal, there is a high possibility that there will be lingering redness, from tape removal, and skin marker ink. This is normal and the redness and ink should fade after a few days.

Research-Related Injury or Inquiry

If you think you have been harmed from this study, please contact Eric Seibel at 206-235-0447.

If you have any questions about the study, please contact one of the researchers listed below:

Shawn Swanson - sshawn@uw.edu

Vivian Luu – vluu2@uw.edu

Joelle Tudor - tudorj@uw.edu

Subject's Statement

This study has been thoroughly explained to me and I have had an opportunity to ask questions. I volunteer to take part in this research. If I have any additional questions or have been harmed by this study, I can contact any of the researchers listed on the first page of this consent form. If I have any questions about my rights as a research subject, I can call the Human Subjects Division at (206)-543-0098 or call collect at (206)-221-5940. I will receive a copy of this consent form.

Printed Name of Subject	Signature of Subject	Date

Copies to: Researcher

Subject

A.5 Clinical Trial Activity Log

Activity Performed	Duration of Activity (can be approximate)	Condition of Tape after Performing Activity