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Chapter 6

Silicone Adhesives in Medical Applications

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Abstract

This chapter will review silicone based adhesive technologies, applications and characterization, emphasizing those self-adhesive materials often used in skin contact applications including transdermal drug delivery and wound care device attachment. The silicone pressure sensitive adhesives used in transdermal applications today are thermoplastic and based on silicone polymer and silicate resin chemistries. Previous research has suggested that some drugs readily diffuse through silicone adhesives, prompting their use in transdermal patches. A recently developed silicone acrylate hybrid adhesive technology combines polyacrylate and silicone molecular structures to form a stable, semi-interpenetrated network. This technology provides ease in formulating transdermal drug delivery systems through improved physical stability over simple blends of acrylate and silicone adhesives. The ability of some silicone adhesives to affix bandages without disrupting the wound bed upon removal has led to the wide acceptance of a third type of silicone adhesive technology that unlike the aforementioned thermoplastic materials is thermoset. This adhesive form is based on a platinum catalyzed, cross-linking reaction between vinyl functional and silicon-hydride functional silicone polymers. The various silicone adhesive types have been characterized *via* classical measurements of physical performances. Rheological techniques elucidated herein provide further understanding of the structure-property relationships previously unavailable using classical characterization approaches.

Keywords: silicone, pressure sensitive adhesive, soft skin adhesive, transdermal, wound care, silicone acrylate, polydimethylsiloxane, semi-interpenetrating network

1. Introduction

The term "silicone" is not always used consistently, and should only be used to refer to polymeric materials, avoiding the relatively common confusion with the metallic element

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silicon (Si). Silicones are synthetic polymers containing Si—O—Si bonds and are used in many industries for their water repellency, ability to wet-out surfaces, high permeability to gases, stability in extreme temperatures, and resistance to thermal, radiation and chemical degradation. The variety of physical forms and physiochemical properties that silicones can display has led to their adoption in a diverse array of healthcare applications including medical devices and as active pharmaceutical ingredients (API) and excipients in medicines for over 60 years [1]. One class of silicone materials that has generated continued interest and research is silicone adhesives, specifically those self-adhering materials that do not require any activation immediately prior to use. Silicone adhesives are used as excipients in transdermal patches, and as skin contact adhesives in prosthetic and wound care device attachment. Recent investigations support the use of silicone based pressure sensitive adhesives for their skin-friendliness, but also to enhance the efficacy of the drug in transdermal drug delivery patch products. Recent silicone technologies like silicone based hybrid pressure sensitive adhesives promise potential performance advantages and improved drug delivery efficacy in transdermal drug delivery systems. Other silicone adhesive types are well known for their atraumatic removal from skin - an ability to remove cleanly from compromised skin without negatively impacting the wound healing process.

This chapter will review silicone based adhesive technologies, applications and characterization, emphasizing those self-adhesive materials often used in skin contact applications. One type of silicone adhesive that is well established in the medical device industry but outside the scope of this work are room temperature vulcanizing (RTV) sealants. While these sealants are an interesting and useful class of materials, they will not be a focus of this chapter. Unlike the self-adhering adhesives discussed in this chapter, once fully crosslinked, the RTV sealants are non-tacky and rubbery and designed to form a permanent bond between substrates. These materials have a similar chemistry to silicone caulks commonly in the construction industry, and have found utility adhering materials to silicone elastomers, bonding parts of medical devices together, and acting as encapsulants and sealants in a variety of medical devices, including pacemakers [2].

2. Silicone chemistry

While the term “silicone” persists in common vernacular, “polyorganosiloxane” is a more appropriate term, and has found acceptance in most scientific literature. Polyorganosiloxanes are organosilicon polymers, the most common of which are the trimethylsiloxy-terminated polydimethylsiloxanes (**Figure 1**) [3].

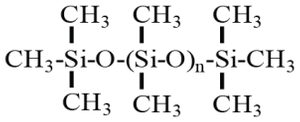


Figure 1. Chemical structure of typical polydimethylsiloxanes.

The silicon in polyorganosiloxanes can be combined with one, two or three organic groups, commonly —CH_3, —$CH{=}CH_2$ or —H, with the remaining valence(s) satisfied with oxygen [4]. Branched silicone structures are made possible by substitution of dimethyl siloxane units (i.e., $(CH_3)_2SiO_{2/2}$) with those that contain additional Si—O connections (e.g., $CH_3SiO_{3/2}$ or $SiO_{4/2}$) [4]. It is through the fact that different siloxane units can be combined with one another in the same molecule that the great variety of silicone compounds arises [3].

Silicones exhibit an inorganic backbone chain $(Si—O)_n$ and organic, (typically methyl) side groups [5]. It is this unusual combination and the resulting physiochemical properties that are responsible for many characteristics of the silicone adhesives. The silicon to oxygen bonds of the backbone are longer and more open than carbon to oxygen bonds permitting the characteristic flexibility of the siloxane chain. By way of comparison, the rotational energy around a —CH_2—CH_2 bond is over four times greater than that of a typical $(CH_3)_2Si—O$ bond. This flexibility is responsible for the characteristic low surface tension observed in silicones which allows them to quickly "wet out" onto surfaces including skin [5].

In addition to increased flexibility, the silicon-oxygen bonds are also stronger than carbon-carbon bonds. The bond energy of a Si—O bond along the backbone of a silicone polymer is 452 kJ/mol while the typical C—C bond of the backbone of an organic polymer is only about 348 kJ/mol [5]. The inherently strong backbone of silicone polymers can help explain the acknowledged chemical stability silicone polymers possess toward a variety of degradation routes including moisture, UV, and a wide range of temperatures. This is equally important at very low and very high temperatures, where some types of silicones maintain their characteristic physical properties and utility from −100°C up to 260°C [6].

Silicones in general, are hydrophobic, (i.e., having little or no affinity for water), so one may anticipate silicones to be extremely lipophilic, given the common perspective equating hydrophobicity with lipophilicity (i.e., having a strong affinity with lipids). However, in the case of silicones, only relatively small silicone polymers are lipophilic. Polydimethylsiloxane (PDMS) polymers in excess of six to eight $(CH_3)_2SiO$ units have little affinity with lipids while larger polymers are essentially lipophobic. These hydrophobic and lipophobic properties impact the ability to solubilize drugs, oils, botanicals and other traditional active ingredients into a silicone matrix [4]. The relatively poor miscibility of silicones with many compounds may be a key to the noted release efficiency of those same compounds from silicones.

3. Silicone pressure sensitive adhesive: description and applications

Silicone pressure sensitive adhesives (PSA) are comprised of high molecular weight silanol-functional silicone polymers and silanol functional MQ siloxane resins. While a simple mixture of silicone polymer and resin can yield an adhesive with adequate peel adhesion and tack properties, sufficient cohesive strength is lacking. The silicone pressure sensitive adhesives most often used in medical applications are the product of a silanol condensation reaction between the polymer and resin components yielding a network structure, commonly referred

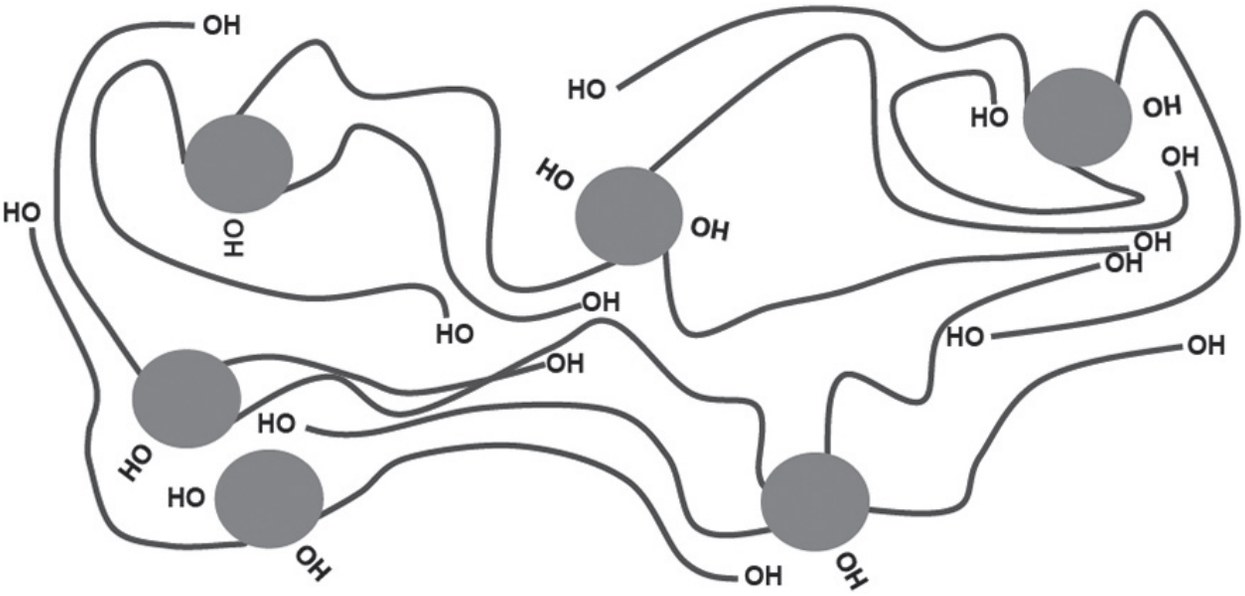


Figure 2. Schematic of the standard silicone PSA.

to as standard pressure sensitive adhesives (**Figure 2**). These materials have suitable cohesive strength for medical device and transdermal drug delivery system applications, and upon removal from the skin the adhesive layer is removed intact. These adhesives are typically supplied in a volatile solvent which is removed during the coating process.

Silicone PSA have a long history of use in transdermal drug delivery systems but may also be used to attach prostheses and wound care devices. One recent innovative example of the utilization of silicone PSA in medical device attachment is the Embrace® MINIMIZE Silicone Scar Aid which consists of a silicone PSA coated onto silicone elastomer (rubber) sheeting. A unique applicator allows the dressing to be applied to relieve tension on healing skin to minimize scar formation [7, 8].

Another application where silicone PSA have found wide acceptance is in the field of transdermal drug delivery. Second to the active pharmaceutical ingredient (API) or drug, the pressure-sensitive adhesive used in a transdermal drug delivery system can be viewed as the most critical component. Without proper and sustained adhesion to the skin, drug delivery from this dosage form does not occur.

Multiple transdermal drug delivery system (TDDS) designs are reported in the literature and are commercially available including reservoir, matrix, and drug-in-adhesive (DIA) systems; slight variants and combinations of each of these patch designs are also found. The functional requirements of the pressure sensitive adhesives in each patch design can vary with the design. (**Table 1**) [9, 10].

Regardless of the patch design, basic requirements for the adhesive that is in direct contact with the skin include sufficient moisture resistance to stay adhered while perspiring and showering and biocompatibility (i.e., the adhesive must be non-irritating and non-sensitizing

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Adhesive functional requirement	Patch construction		
	Matrix with rim adhesive	**Reservoir with rate controlling membrane/face adhesive**	**Drug-in-adhesive**
Biocompatibility	+	+	+
Moisture resistance	+	+	+
Acceptable tack	+	+	+
Good adhesion	+	+	+
Good cohesive strength	+	+	+
Adherence to backing layer	+	+	+
Adherence to rate controlling membrane		+	+ (in some cases)
Compatible with drug and excipients	+ (in some cases)	+	+
Permeable to drug and enhancers		+	+
Cold flow resistance	+ (esthetic only)	++	++
Stabilize drug and excipients			+

Table 1. Adhesive functional requirements for common transdermal patch designs.

at a minimum). The adhesive must also have acceptable tack to adhere quickly on contact, good wetting behavior to achieve sufficient adhesion for the duration of wear (typically from 12 h to 7 days) and possess sufficient cohesive strength to enable removal without residual adhesive remaining on the skin. In most transdermal patch designs, the adhesive must also resist cold flow, or creep, the property of an adhesive to deform, especially at ambient temperature prior to use or at skin temperature when in use.

The TDDS design with the most straightforward adhesive requirements is a matrix patch with a rim adhesive layer around the periphery of the patch. In this type of patch design, the adhesive functions are not significantly different from other device attachment applications as the adhesive must simply adhere the patch to the skin for the intended wear period. If the rim adhesive layer comes into contact with the drug loaded matrix layer, the adhesive must also be compatible with the matrix layer components. Resistance to cold flow for a rim adhesive is esthetically pleasing but does not result in unintended drug exposure or impact the drug contact surface area, so is not usually a mandatory function.

Reservoir patch designs are typically characterized by a liquid reservoir compartment with solubilized API separated from the skin contact PSA by a semipermeable membrane. For a reservoir patch design with an adhesive layer across the face of the entire patch, the adhesive must adhere to the membrane and provide adequate adhesion to skin, as well as be compatible with the drug and allow diffusion of the drug and any penetration enhancers to the skin interface. The adhesive properties must be resilient to the drug and enhancer(s) reaching saturation in the adhesive layer.

In a drug-in-adhesive (DIA) patch design, the adhesive plays an even greater role in the overall function of the patch. While this type of patch construction is clearly the easiest to manufacture, many formulation challenges exist, particularly with a monolithic (i.e., single layer) design. In addition to the requirements stated above, the adhesive matrix must also stabilize the API and excipients in either a dissolved or dispersed state, and allow controlled release of the drug and enhancers. Cold flow reduction is even more challenging in monolithic patch designs too, as they commonly require a greater adhesive coat weight than constructs that use face adhesive layers.

It is unlikely that any single, off the shelf, adhesive system can meet the demands for all patch formulations and patch types. Silicone PSA, along with acrylic and polyisobutylene (PIB) PSA, are commonly used in transdermal patch applications. The end-use properties of silicone PSA (tack, adhesion, cohesive strength) can easily be modified or customized by varying the resin-to-polymer ratio, the degree of cross-linking and the residual silanol functionality during preparation. Silicone PSA are soluble in a variety of volatile polar and non-polar hydrocarbon solvents and additional customization may be achieved *via* the solvent in which the silicone PSA is dispersed as well as the concentration of the PSA in solvent. Solvent and concentration may be matched to provide optimal conditions for drug and excipient dissolution for TDDS manufacturing. Hot melt forms of silicone adhesives are also available. The capability to uniquely customize silicone PSA is essential for use in transdermal drug delivery applications and is likely responsible for their use therein. There are instances where more customization is required than can be achieved with standard silicone adhesives. For the silicone chemistry described above and noted in **Figure 2**, it is important to note that exposure to amines and amino-functional drugs and excipients will cause certain silicone PSA to lose tack and their ability to instantly adhere to the skin. Standard silicone PSA can be chemically treated to reduce the silicon-bonded hydroxyl (silanol) content of the adhesive to render the PSA resistant to loss of tack, commonly referred to as amine-compatible silicone adhesives (**Figure 3**) [11].

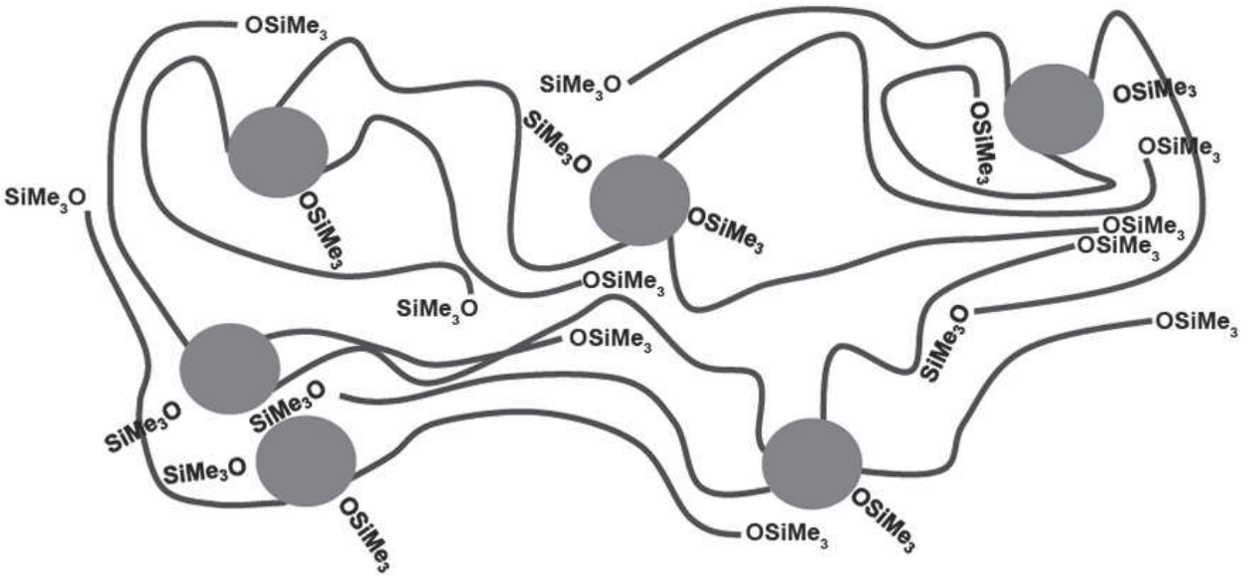


Figure 3. Schematic of amine compatible silicone adhesives.

Silicone PSA is utilized in a variety of marketed TDDS either as the primary adhesive system or in combination with acrylic adhesives. **Table 2** provides a list of commercial TDDS that utilize silicone PSA as a component of the patch construction as of the time of this publication, the respective actives, and other relevant information is also included. The table highlights the evolution of TDDS designs from the first silicone-containing reservoir patch in 1981 to recent approvals of more sophisticated microreservoir and multilayer designs that incorporate different adhesive types to achieve demanding dosage requirements.

In recent years, the nomenclature for silicone PSA listed in the FDA Inactive Ingredient Database (IID) has been standardized to allow patch formulators to more easily identify prior use and maximum potency. Previously, reference to the use of silicone PSA in transdermal patches varied from a description of an adhesive laminate to numeric product codes. The preferred substance name for standard silicone adhesives is now dimethiconol/trimethylsiloxysilicate crosspolymer, and the preferred substance name for amine-compatible silicone adhesives is trimethylsilyl-treated dimethiconol/ trimethylsiloxysilicate crosspolymer. Reference is made to various types of adhesive with the addition of a nominal resin/polymer ratio [12].

Drug	Patch	Marketer	Construction	Silicone PSA components
Nitroglycerin (1981)	Transderm-Nitro®	Novartis	Reservoir	Silicone face adhesive layer
Fentanyl (1990)	Duragesic®	Janssen Pharms	Reservoir	Silicone face adhesive layer
Estradiol (1996)	Vivelle-Dot®	Novartis	Microreservoir monolithic matrix	Silicone matrix adhesive continuous phase with acrylate polymer microreservoirs
Nicotine (1997)	Generic (OTC)	Aveva	Multilayer matrix	Silicone matrix adhesive continuous phase with acrylate face adhesive
Estradiol / Norethindrone Acetate (1998)	CombiPatch®	Noven	Microreservoir monolithic matrix	Silicone matrix adhesive continuous phase with acrylate polymer microreservoirs
Fentanyl (2005)	Generic	Mylan Technologies	Drug-in-adhesive monolitic	Silicone matrix adhesive continuous phase
Fentanyl (2006)	Generic	Lavipharm Labs	Multilayer matrix w/ membrane	Silicone matrix adhesive, continuous phase and face adhesive layer

Drug	Patch	Marketer	Construction	Silicone PSA components
Methylphenidate (2006)	Daytrana®	Noven	Microreservoir monolithic matrix	Silicone matrix adhesive continuous phase with acrylate polymer microreservoirs
Fentanyl (2007)	Generic	Actavis Labs	Reservoir	Silicone face adhesive layer
Fentanyl (2007)	Generic	Mayne Pharma	Reservoir	Silicone face adhesive layer
Rivastigmine (2007)	Excelon® Patch	Novartis	Multilayer matrix	Silicone face adhesive layer
Rotigotine (2007)	Neupro®	UCB	Microreservoir monolithic matrix	Silicone matrix adhesive continuous phase
Capsaicin (2009)	Qutenza®	Acorda	Drug-in-adhesive monolitic	Silicone matrix adhesive continuous phase
Clonidine (2009)	Generic	Aveva	Multilayer matrix w/ membrane	Silicone matrix adhesive continuous phase with acrylate face adhesive
Fentanyl (2011)	Generic	Mallinckrodt Inc	Multilayer matrix w/ membrane	Silicone matrix adhesive, continuous phase and face adhesive layer
Estradiol (2012)	Minivelle®	Noven	Microreservoir monolithic matrix	Silicone matrix adhesive continuous phase with acrylate polymer microreservoirs
Estradiol (2014)	Generic	Mylan Technologies	Microreservoir monolithic matrix	Silicone matrix adhesive continuous phase with acrylate polymer microreservoirs

Table 2. Commercial TDDS patches utilizing silicone PSA.

4. Silicone and acrylate adhesive blends

Silicone and acrylic PSA chemistries as well as combinations of the two are commonly utilized in transdermal drug delivery [13]. The selection of the adhesive is typically drug and TDDS design specific and each adhesive type has its own advantages and disadvantages. Silicone adhesives may be more challenging during patch formulation due to the immiscibility with

many drugs and common excipients in the silicone matrix; while acrylic adhesives are often easier to formulate due to the increased solubility of drugs and miscibility of excipients. However, higher drug utilization is often observed from TDDS that employ a silicone PSA over comparable patches that use an acrylic PSA [13, 14]. Yeoh [14] has provided a review of marketed fentanyl patches and has shown patches utilizing silicone adhesives have much greater fentanyl depletion during use and lower residual drug content after their intended use than comparable patches that use an acrylic adhesive. Minimizing the amount of residual drug in the patch at the end of the labeled use period, particularly with opiate drugs, is a focus of a recent FDA Guidance [15].

Combining silicone and acrylic pressure sensitive adhesives to form an immiscible polymer blend can provide benefits for transdermal drug delivery through selective modification of the solubility and/or diffusivity of the drug in the polymer blend matrix [16]. These micro-reservoir systems allow the drug to be solubilized in high concentrations in the discontinuous polyacrylate phase [17] and have been shown to be beneficial in decreasing patch size and required drug loading [18]. This technique has been successfully implemented in several commercial transdermal patches on the market including CombiPatch®, Daytrana® and Minivelle® (Noven Pharmaceuticals) as well as Vivelle Dot® (Novartis Pharmaceuticals) [16] A review of label claims for two patches that provide a 0.5 mg/day dose of estradiol reveals that a 5 cm^2 Vivelle Dot® patch, which employs the Dot Matrix® technology, can deliver 22.4% of the drug, whereas the 12.5 cm^2 Climera® with an acrylic PSA construction only delivers 9.0% of the drug [19]. These immiscible blends do have a major limitation in that they will exhibit macro phase separation in the coating mass if mixing is discontinued which may be exacerbated upon addition of other formulation ingredients such as penetration enhancers [20]. One potential means to prevent macro phase separation of the two immiscible adhesives is to covalently link the two polymer chemistries together, creating a silicone-acrylate hybrid material.

5. Silicone-acrylate hybrid

Hybrid adhesives, in which silicone and acrylic chemistries are combined, have been described following different routes [21, 22]. One approach is the reaction product of a (meth)acrylate-functional silicone PSA and ethylenically unsaturated monomers, [21] whereas a second route toward a hybrid adhesive describes an alkoxysilyl-functional acrylic prepolymer that is further condensed or "bodied" with silicone PSA precursors (i.e., OH-functional silicate resin and OH-terminated PDMS) in the presence of a condensation catalyst [22]. These hybrid adhesives, although produced *via* opposite approaches, likely have the potential for making very similar materials depending on the exact formulation and extent of covalent coupling between the acrylate and silicone phases. As with the simple blends of silicone and acrylic adhesives mentioned above, the hybrid materials result in an immiscible matrix and exhibit a typical domain (droplets of incompatible material) in continuous phase appearance. However, unlike simple blends, the hybrid adhesives are capable of much finer domain sizes and demonstrate superior phase stability during formulation and in a cast film as shown in **Figure 4** [20].

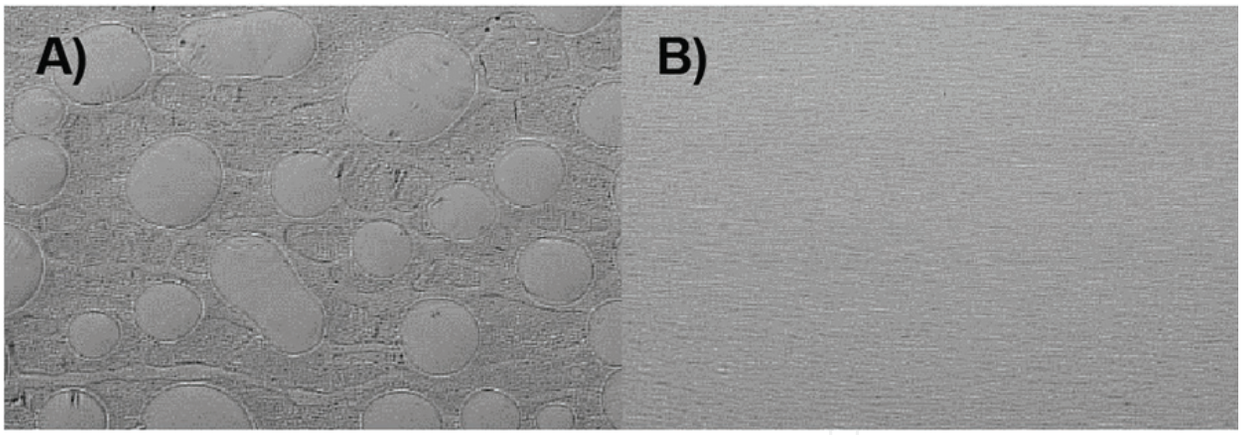


Figure 4. Optical micrograph (100X magnification) of (A) 50:50 blend of silicone PSA and non-functional acrylic PSA and (B) silicone-acrylate hybrid adhesive (50% acrylate) [20].

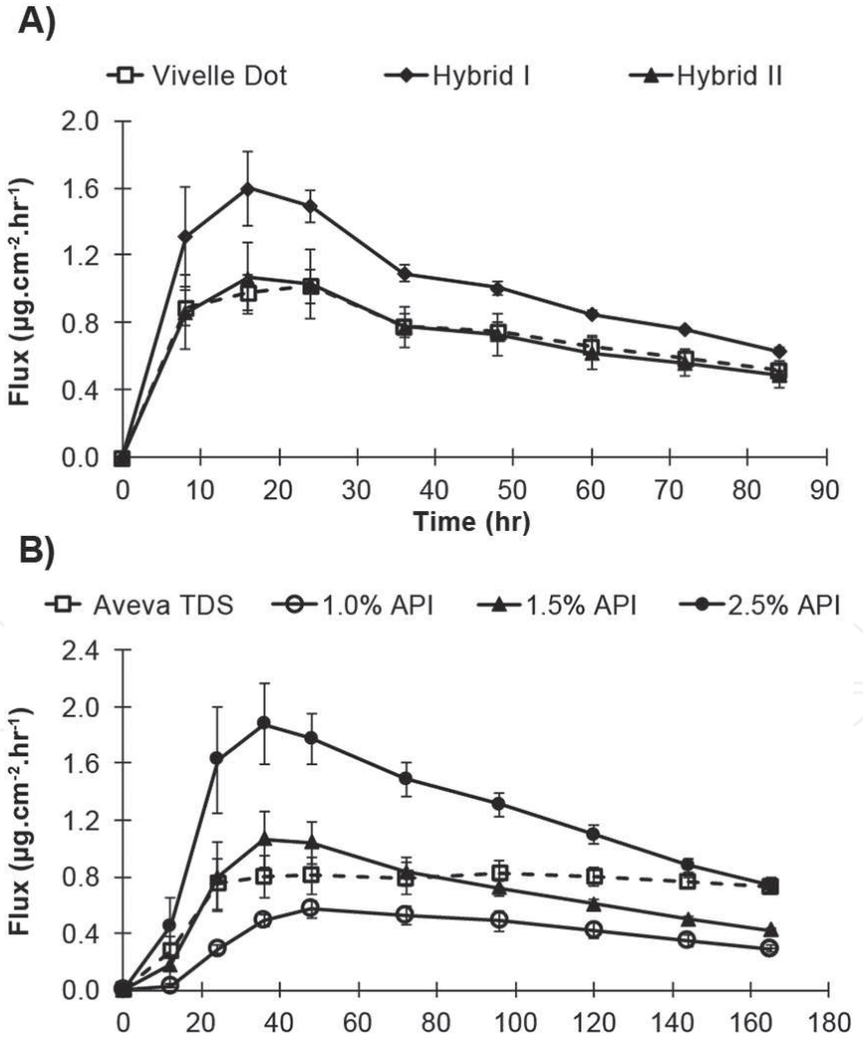


Figure 5. Drug flux from silicone-acrylate hybrid PSA based patches; (A) estradiol 1.5 wt%; (B) clonidine at 1, 1.5 and 2.5 wt%; [23].

Drug delivery using silicone-acrylate hybrid adhesives (SilAc I and SilAc II) differing in the ratio of high and low T_g acrylic monomers has been reported, and delivery of estradiol (**Figure 5A**), clonidine (**Figure 5B**), and ketoprofen was demonstrated across human cadaver epidermis from these matrices. The authors also noted that the use of silicone-acrylate hybrid PSA, singularly or as blends with silicone PSA resulted in a more desirable wet blend compatibility/stability than those obtained with blends [23].

Due to the inherent immiscibility of silicone and acrylate polymers, the hybrid adhesives contain micro-domains which can be observed using transmission electron microscopy (TEM) as presented in **Figure 6**. Further analysis of the phase behavior reveals the ability to selectively control the domain arrangement (i.e., silicone-in-acrylate or acrylate-in-silicone) of these materials by the choice of casting solvent, with the phase having the highest affinity with the casting solvent remaining external, (i.e., heptane casting solvent exhibiting a silicone continuous phase and polyacrylate discontinuous phase (**Figure 6A**) or *vice versa*, (**Figure 6B**)). Phases can also be controlled through changing the volume fraction of silicone or acrylate through blending or addition of specific co-solvents.

The selective control of the phase arrangement provides potential options for tuning both the adhesive properties as well as tailored drug release profiles as illustrated in **Figure 7**.

The impact of casting solvent and silicone content on the material properties has been conducted using a dynamic rheometer (**Figure 8A**). Blends of silicone PSA and silicone-acrylate hybrid PSA (nominally 50% silicone) were prepared in either heptane or ethyl acetate to yield a range of materials. For materials delivered from ethyl acetate, between 76% and 78% silicone, a precipitous change in tan delta is observed followed by incremental decrease as the silicone content rises. Tan delta is a rheological property that approximates the internal friction of a material. When tan delta is greater than one, a material is more viscous than elastic,

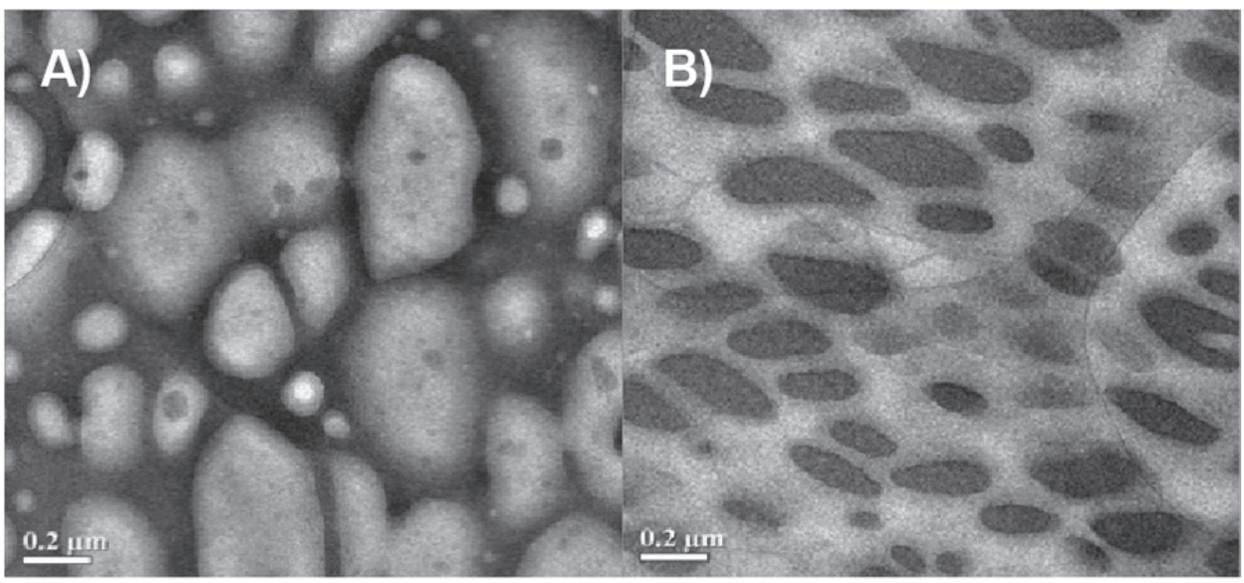


Figure 6. Transmission electron micrograph of silicone-acrylate hybrid adhesive films, silicone phase appears dark due to the electron density (A) cast from heptane and (B) cast from ethyl acetate.

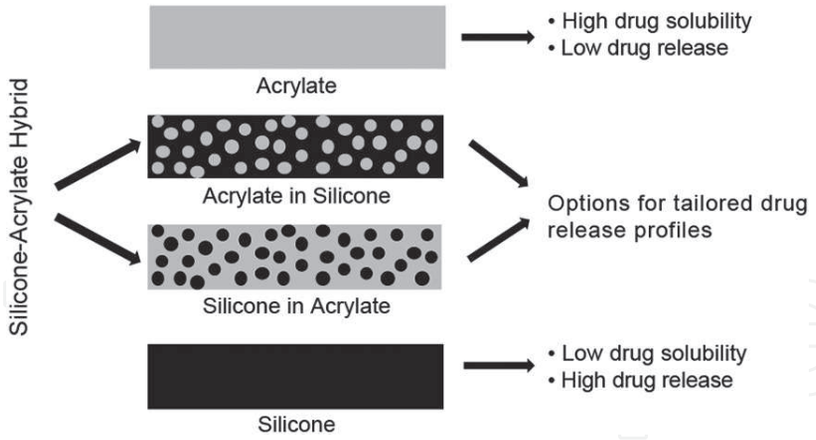


Figure 7. Illustration of silicone-acrylate hybrid adhesive microstructure and potential impact on drug solubility and release.

and when it is less than one it is more elastic than viscous. TEM analysis suggests this is the result of phase inversion when the silicone becomes the external phase. This change is not observed for materials delivered from heptane as the silicone remains the external phase over the entire range. Films containing either 1.0 wt% estradiol (**Figure 8B**), 2.5 wt% ibuprofen (**Figure 8C**), or 2.5 wt% lidocaine (**Figure 8D**) were prepared using blends of hybrid PSA

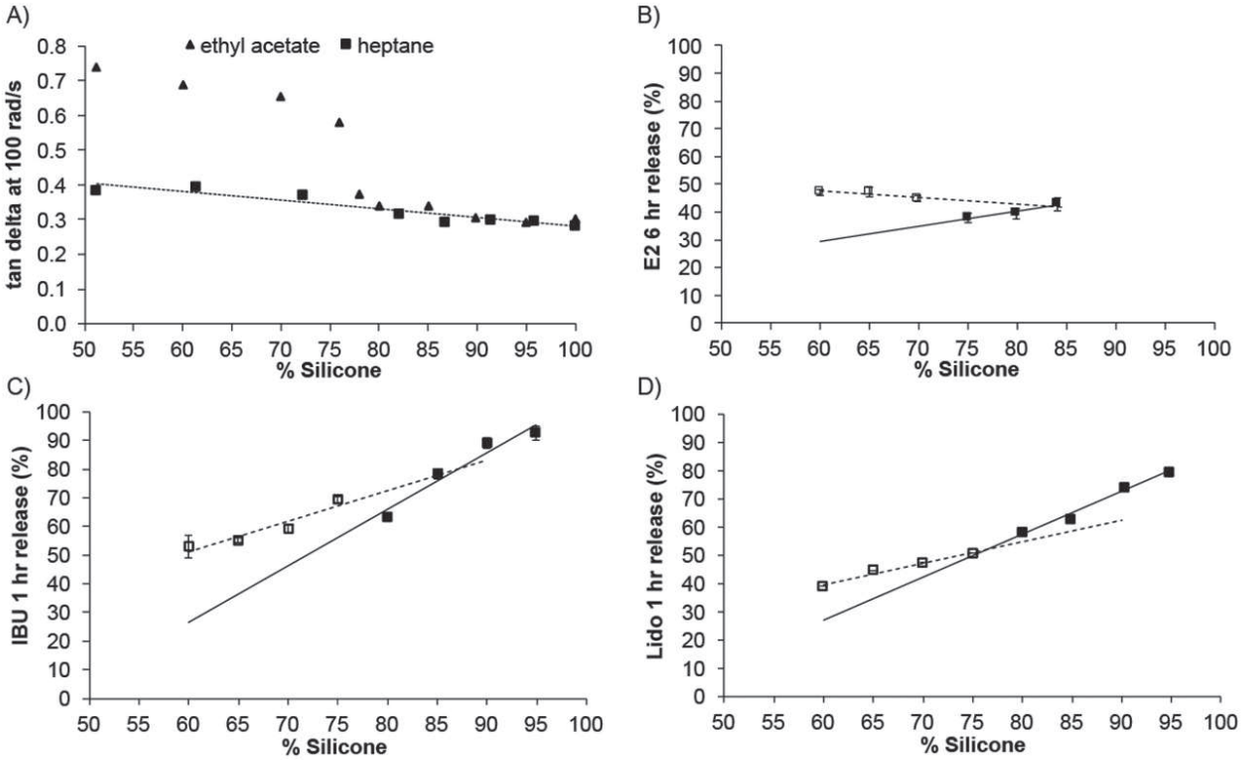


Figure 8. Rheology and drug release as a function of silicone content and dispersion solvent; (A) tan delta of the adhesive matrix; (B) estradiol (E2) 6 h cumulative release; (C) ibuprofen (IBU) 1 h cumulative release; (D) lidocaine (Lido) 1 h cumulative release [24].

with silicone PSA to investigate the impact of phase arrangement on the release behavior. All three API demonstrate a change in drug release characteristics between 75 and 80% silicone content, which is where rheology suggests the phase inversion occurs [24].

6. Silicone pressure sensitive adhesive: strength characterization

The characterization of PSA materials is a critical part of innovation development and production quality control. Historically, tape properties such as peel adhesion, shear and tack have been used to characterize the performance of pressure sensitive adhesives targeted for transdermal applications. However, these tests often have high variability resulting in wide specification limits and poor correlation of test data with adhesive performance in real life applications [25]. Furthermore, tape property tests can be substrate dependent. That is to say, they are influenced by the substrate on which the PSA is coated and also by the substrate on which the adhesive performance is measured. Despite the drawbacks of tape property testing, they are still commonplace and so, warrant some discussion.

Peel tests are well described in the literature and are common to the majority of adhesives. The peel test typically occurs at 90° or 180° and the force to remove the adhesive from a substrate (e.g., stainless steel in many cases) is measured. In the case of silicone PSA, the typical adhesive thickness tested is relatively thin, commonly between two and five mil (approximately 51–127 micron). A distinction between peel adhesion and tack of an adhesive is often made. From an analytical test perspective, the distinction between peel adhesion and tack measurements is the time allowed for the adhesive to bond with the substrate. When measuring tack, the measurement is taken almost instantaneously after the adhesive comes in contact with the test substrate, whereas peel adhesion is measured after the adhesive is left in contact with the substrate for a longer time period. The time between application and testing allows the adhesive to wet out on the surface and the adhesion to build.

Shear testing may have greater relevance to skin contact adhesive applications than the aforementioned peel adhesion and tack tests. Since PSA are condensed materials that have the ability to flow, the extent of cold flow must be characterized to fully understand and anticipate the surface area of adhesive in contact with skin, which can impact the amount of drug delivered from a transdermal patch. Shear tests of fully formulated adhesive matrices may be even more relevant to the performance of the final TDDS. If the skin/adhesive interface changes over time, the transdermal drug diffusion will also change. Typically, a shear test is the measurement of the time for the adhesive to detach from a surface (e.g., stainless steel) under a constant weight.

The advantages of tape property test methodology include ease of set up, reproducibility and a straightforward interpretation of data. However, drawbacks including the considerable influence adhesive coating thickness has on the test, the influence of the substrate on which the adhesive is coated, and the surface on which the test is conducted must also be rationalized. To minimize these influences, there must be accurate control of adhesive thickness and standardization of substrates and test surfaces.

7. Silicone pressure sensitive adhesive: rheology

Although tape property testing may qualitatively predict how quickly a system may bond to a substrate, the extent to which the adhesive resists cold flow, and how much force may be needed to remove it, and perhaps most importantly, the wear performance of the system may not be adequately addressed using classical characterization techniques. In order to better understand and predict the wear performance of transdermal systems, rheology is often used to understand the adhesive bulk viscoelastic behavior. [26] Rheological characterization allows the analyst to overcome the inherent uncertainty linked to peel, tack and shear tests by minimizing the influence of sample preparation and substrate variability on adhesive characterization results. Rheology is a technique to characterize viscoelastic properties of polymers and also predict wear performance of pressure sensitive adhesives. As shown below in **Figure 9**, a typical rheological curve can be correlated to tape properties [27–30].

Data have shown that for viscoelastic materials, such as silicone pressure sensitive adhesives, frequency sweep curves are sensitive to structural differences (e.g., crosslink density) and formulation changes (e.g., resin-to-polymer ratio). This sensitivity provides a means to identify, characterize and predict adhesive wear performance [26].

Storage modulus (G′) is an indicator of how elastic the adhesive is and how much energy is stored during deformation, while the loss modulus (G″) indicates the viscous component of the PSA and how much energy is lost as heat, while complex viscosity (η*) is an indicator of the adhesive bulk viscosity and can be related to the cold flow [25]. Bonding of a transdermal system occurs at a low deformation rate, and is dependent on the wetting behavior of the adhesive when it comes into contact with skin [26]. Rheologically, the storage modulus, G′, values at low frequency may be used for predicting wetting and creep (cold flow) resistance. Optimum wetting occurs when the adhesive modulus is low. Subsequently, debonding of a transdermal system occurs at high deformation rates [26].

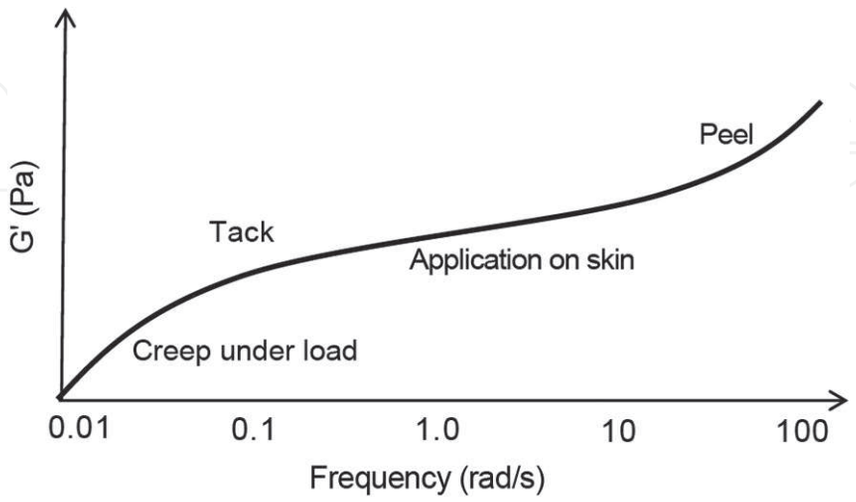


Figure 9. A schematic representation of the link between the rheological profile and the final pressure sensitive (PSA) wear performance [25].

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Rheologically, the storage modulus, G′, and loss modulus, G″, at high frequency may be related to the peel adhesion and quick stick (i.e., tack) properties of an adhesive and the subsequent TDDS [31, 32]. For bonding, the viscous contribution should be higher than the elastic contribution to the PSA viscoelastic profile. In rheological terms, this means that at low frequencies, G′ < G″ and the opposite for the debonding step, represented at high frequencies where G′ should be equal to or higher than G″. Based on this interpretation, the rheological traces in **Figure 10** suggest that the increase of resin content should lead to reduced cold flow (i.e., an increase of the complex viscosity with resin content) and an increase of the adhesion strength (i.e., increase of both G′ and G″ with resin content). Dynamic frequency sweeps (0.01–100 rad/s) were conducted on dried adhesive solids using a TA ARES-G2 rheometer. The adhesives with high and medium resin content were tested using 8 mm parallel plates, at 0.35% and 0.5% strain respectively. The adhesive with low resin content was tested using 25 mm plates, at 0.5% strain. All samples were tested at 30°C with a 1.5 mm gap.

In the early 1990s, E.P. Chang developed a theory to interpret rheological data of pressure sensitive adhesives and establish criteria for PSA classification when used in conjunction with the Dahlquist's criteria [33]. This theory is now well known as "Chang viscoelastic window." As depicted in **Figure 11**, a G′ vs. G″ graph, is divided into four quadrants with a central axis. The location of the analyzed PSA within this graph allows a straightforward extrapolation from rheological properties to real-world adhesion performance. For example, the top right hand quadrant corresponds to high modulus and high dissipation. Therefore, materials in this quadrant with characteristically high G′ modulus compensated by the high G″ are anticipated to be adhesive materials with high adhesion but low tack and high shear

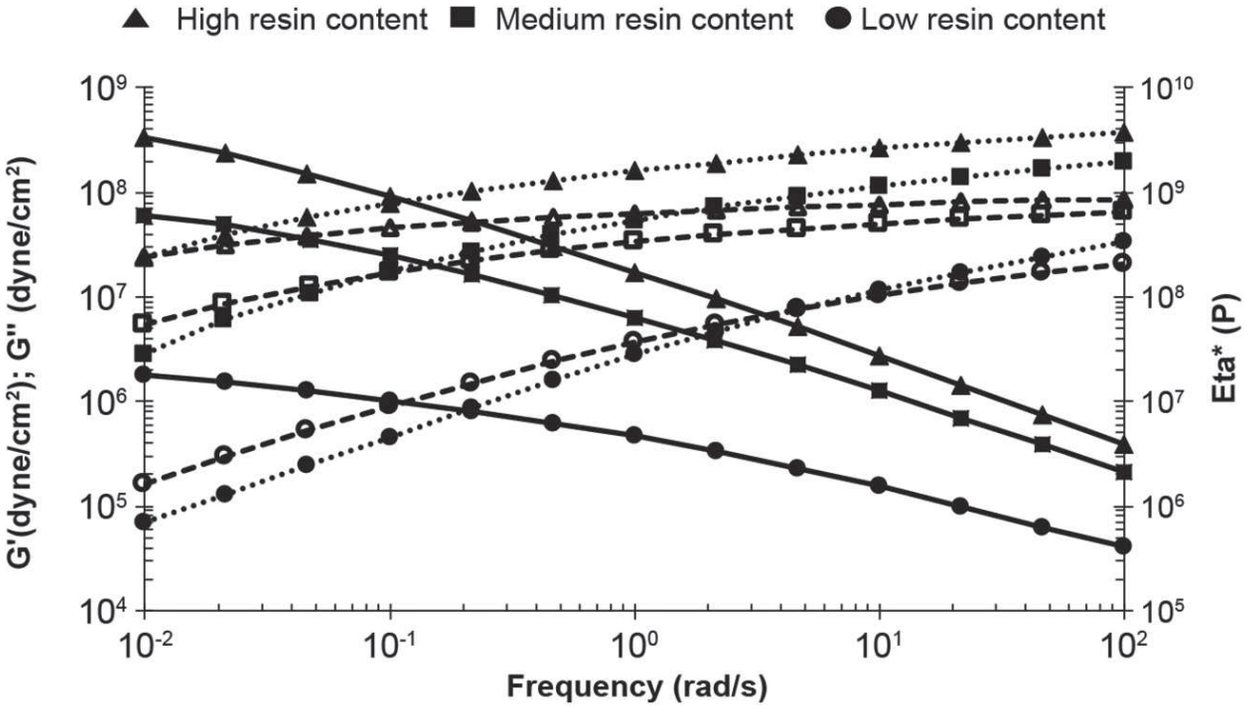


Figure 10. Typical frequency sweeps of silicone PSA at three common resin contents.

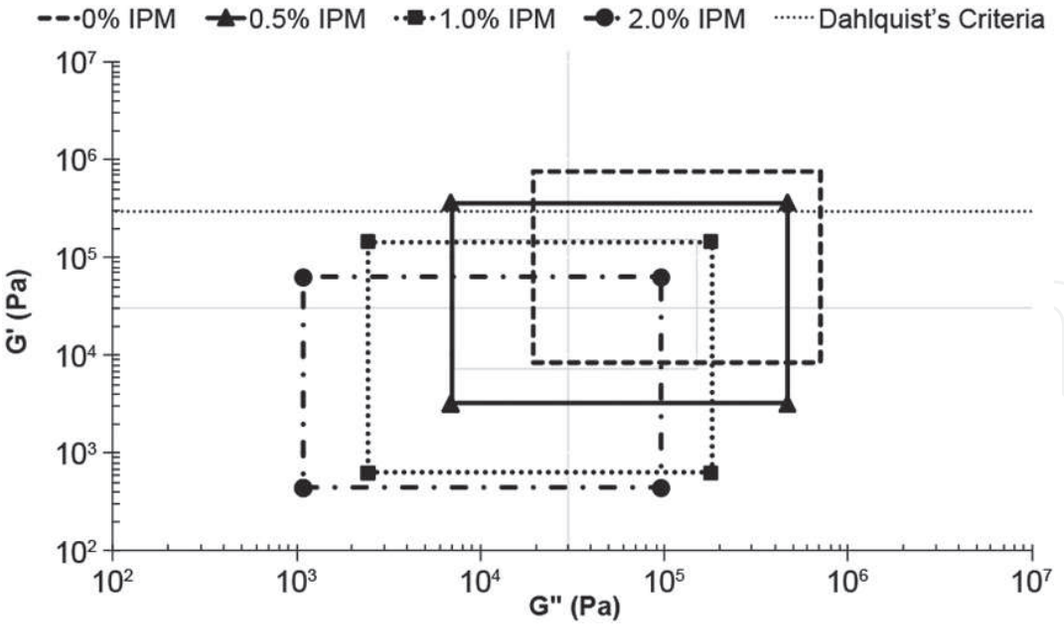


Figure 11. Chang viscoelastic window concept adapted for low resin content silicone pressure sensitive adhesive (PSA) with differing amounts of isopropyl myristate (IPM) [34].

resistance. Conversely, the bottom left quadrant corresponds to low modulus and low dissipation; these materials, are anticipated to exhibit low peel values because of the comparatively low debonding cohesive strength and low dissipation.

Changes in the Chang viscoelastic window, of a typical low resin content silicone PSA can be observed as differing amounts of a commonly used permeation enhancer, isopropyl myristate (IPM), are added (**Figure 11**) [34]. The Chang viscoelastic window of the neat adhesive moves from the upper right quadrant to the lower left quadrant as more IPM is added. The lowermost edge of the window which is linked to bonding of the adhesive is far below Dahlquist's criteria, so the adhesive would be expected to have reasonable tack. There is a significant shift in the position of the upper right corner as IPM content increases which is linked to debonding (peel) efficiency suggesting that an increase of IPM content decreases peel efficiency [34]. Finally, the window size increase indicates a decrease of the PSA shear strength likely due to better solvent compatibility in the PSA. These data coincide with observed changes in adhesive properties as plasticizing agents like IPM are added and support the further use of rheological measurements to characterize changes in wear properties.

8. Silicone soft skin adhesive: description and applications

Silicones have more than 30 year history of safety and efficacy in advanced wound care applications. Much of the success of silicones in wound care is due to an adhesive technology referred to in the literature by many names including soft skin adhesives (SSA), tacky gels, silicone gels and silicone tacky gels among others [35]. The technology was introduced to

the wound care market by Dow Corning Corporation in the 1990s and similar materials are offered today by many silicone suppliers under a variety of brand names [36–38]. In a segment that was historically controlled primarily by acrylic adhesives, the tacky gel technology concept was disruptive by securing wound dressings while providing gentle adhesion upon removal. SSAs have become the material of choice in many advanced wound care applications, due to their reliable adhesiveness, while being easier to remove and causing less pain than many other adhesive technologies of the day.

SSAs are based on a polydimethylsiloxane network which supports the critical adhesive attributes required for securing the device in place and removing it without leaving residue or damaging the skin. Unlike silicone PSAs that build their adhesiveness on a viscous phase bodied with a silicate resin, SSAs are based on the silicone elastomer technology modified to deliver the relevant visco-elastic profile. They also differ from analogous silicone elastomers (e.g., liquid silicone rubber (LSR) technology) by the absence of reinforcing silica filler. As a result, they have a similar consistency to gels, but SSAs are not a typical polymeric gel because they are not based on an insoluble polymer network swollen with fluids. The visco-elastic behavior of SSA also differs from silicone PSA, despite their low consistency and a high degree of compressibility, SSAs show resilience and quick recovery under cyclic deformation [35].

The pressure sensitive adhesive property of SSAs are based on the capacity of the elastomer surface to quickly wet the skin and conform to skin irregularities without an additional compression step as required for a silicone PSA [35]. Thanks to the low intensity of the viscous component of the SSA rheological profile, the adhesive does not flow significantly, and very little dissipation of the energy occurs when deformation pressure is applied to the SSA. As a result, SSA debonding happens at low peel force, without skin stripping and painful skin pulling when the adhesive device is removed. Being elastomeric by nature, SSAs have a low viscous component that limits their flow and consequently the ability to pick up materials on or from the surface of the skin [35]. Therefore, unlike silicone PSA, the adhesive surface of SSAs remain relatively clean upon removal from the skin, allowing for removal and easy reapplication of the dressing or device to the skin, making wound dressing repositioning possible.

The elastomeric structure of SSAs is obtained by cross-linking a network of polydimethylsiloxane (PDMS). The reaction is based on an addition reaction (hydrosilylation) between vinyl functional PDMS (polymer) and hydrogen functional siloxanes (cross-linker) as shown in **Figure 12**. The cure reaction is catalyzed by a platinum complex, which can occur at room temperature or be accelerated at elevated temperature (80–145°C), without the formation of reaction by-products [35]. As thermoset materials, SSAs have a low susceptibility to cold flow and plasticizing effects.

The SSA technology has been extensively used in scar treatment and advanced wound management, demonstrating safety and efficacy recognized by wound care professionals [35]. The use of SSA may be recommended when designing medical adhesive devices, tapes, bandages, drapes, and wound dressings and have been noted for the many benefits including high tack for quick bonding to skin, reliable adhesiveness and cohesiveness, gentle adhesion to fragile and compromised skin, no skin stripping and pain-free removal of the device, as well as permeability to moisture and gases (e.g., CO_2, O_2) [35].

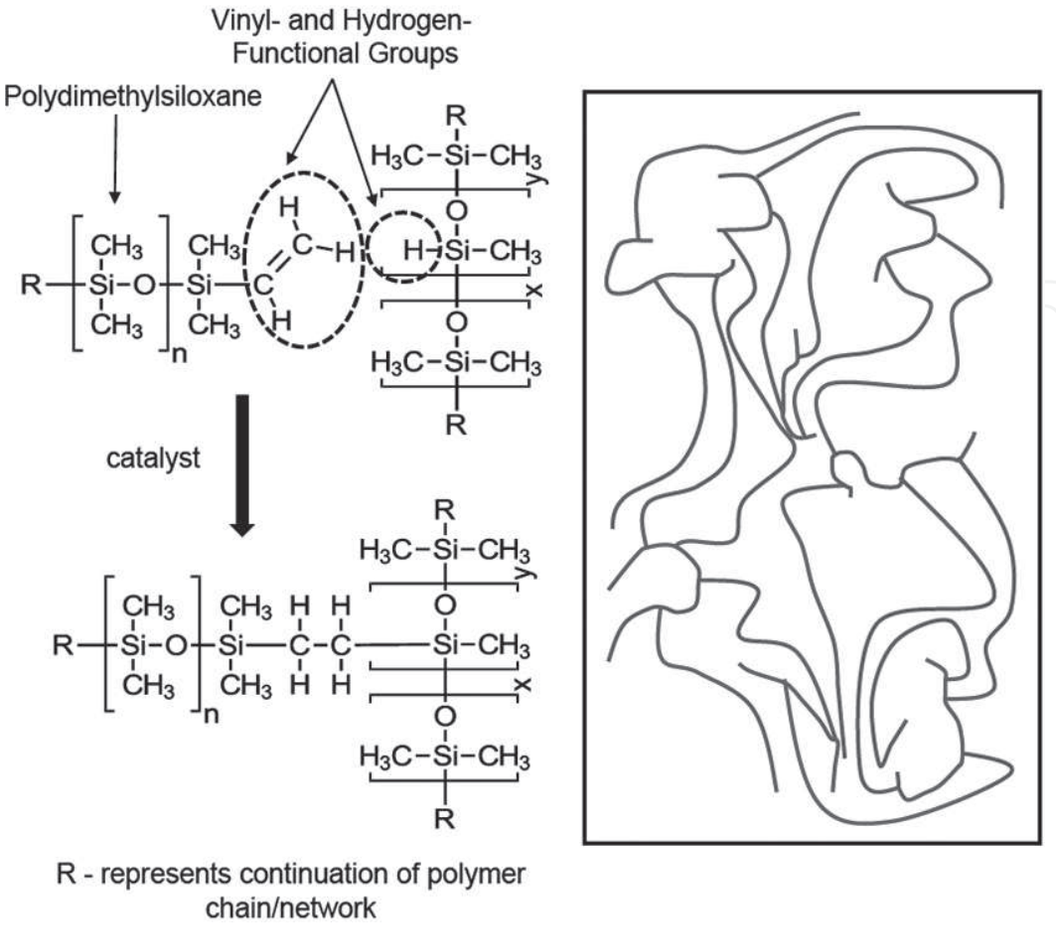


Figure 12. Typical hydrosilylation reaction schematic.

SSAs are supplied as two-part systems with the catalyst in one part and the cross-linker in the other. The materials are characteristically transparent before and after curing into a solid matrix. They are typically processed by mixing the two parts and coating the mixture directly onto the final substrate (i.e., backing film), understanding that this film must be impermeable enough to prevent the uncured liquid SSA from wicking through. The typical coat weight for SSA can vary widely depending on the desired final properties, but often range between 150 and 250 g/m^2. The curing phase is typically completed at elevated temperature adjusted according to the temperature sensitivity of the substrate. After cooling, the adhesive surface is protected by a release liner which is peeled off when the end user applies the adhesive to skin.

Substrate selection is important when designing an adhesive device based on SSA, as the nature of the substrate can significantly impact the coating and cure conditions during the manufacturing phase. The anchorage of the adhesive to the substrate and the cohesion of the adhesive after cure, as well as the ultimate wear behavior of the device when applied to the body can all be impacted by the substrate selection.

The choice of release liner is also a critical factor as it can affect the device stability, making it unusable if this protective film cannot be easily removed from the adhesive prior to use. Traditional silicone release liners that are used ubiquitously with acrylic adhesives cannot be

used with SSA as the silicone release liner chemistry is similar enough to SSA that they are highly likely to interact and experience an irreversible lock-up effect upon storage. However, uncoated polyethylene films, especially LDPE (low density polyethylene) grade, can provide an acceptably low and reasonably consistent release force from the SSA [39].

New SSA technology are being developed that can achieve higher adhesion and longer wear times as well as improved drug compatibility to address emerging medical system market trends including wearable devices and topical drug delivery patches [35]. The use of SSA technology to formulate drug delivery matrices enables drug delivery system designs which address the needs for secure and gentle fixation to fragile, sensitive or compromised skin conditions common in dermatology, wound care, pediatrics and gerontology. Several studies were conducted to evaluate the compatibility of various drugs and their release from SSA matrices. A variety of API have been studied including those indicated for pain relief and local anesthesia, antibiotics, and dermatological actives [39]. Wound care products that utilize silicone tacky gels as the skin contact adhesive and are loaded with chlorhexidine gluconate and other antimicrobial agents have also been investigated [40]. This may signal further interest in the utilization of SSA in even more advanced active-loaded therapies in addition to the traditional wound therapies where it has been used historically.

9. Soft skin adhesive: characterization

Many of the analytical techniques used to characterize silicone PSA have been modified to characterize the SSA materials, although shear tests are less emphasized for SSA due to the characteristically low cohesion of the SSA. In addition to adhesive peel measurements, the measurement of the softness of the SSA by penetration test is often performed. Over a broad range, the penetration measurement shows correlation to adhesion performance values within a formulation type and is linked to the adhesive network chemistry; therefore, it is often used as a quality control measurement.

Peel tests are commonly used in the adhesive industry, because for many applications these relatively easy to perform tests fit well with the final application of the adhesive. The substrates upon which most adhesives are tested to evaluate adhesive strength (e.g., stainless steel) often are not predictive of the relative strength SSA will exhibit in practice on skin. Therefore, some users have resorted to using substrates that have a surface energy more similar to that of skin as the test substrate for SSA. The number and diverse composition of substrates including plastic films, paper and even artificial skin materials, make standardization across the industry difficult, and comparison between users problematic. Testing is conducted similarly to that described for PSA, with the SSA typically being cast and cured at a consistent thickness directly onto a film. This substrate may influence the peel adhesion result due to its intrinsic elasticity and also potentially through interactions with the SSA. The gel on the backing substrate is then applied on a test substrate, taking care to apply the adhesive with a constant force. After a designated equilibration time, the adhesive is peeled from the substrate, typically at a 180° angle, and the force required to remove it is measured.

While this method provides relative adhesion strength, allowing comparison of adhesive values, the results may be significantly influenced by the backing substrate, as well as the test substrate used, so the results do not necessarily simulate the application of the adhesive to skin.

10. Soft skin adhesive: rheology

Rheological measurements have been developed and used for decades to characterize silicone PSA and provide more realistic predictions of real-world adhesive performance than classical peel tests are capable of providing. Recently, similar rheological measurements have been applied to characterize the intrinsic properties of the SSA and offer a characterization method more capable of harmonization across the industry. The SSA rheological characterization is performed on free standing gels and is able to characterize the adhesive properties without the influence of backing or test substrates unlike the aforementioned adhesion tests. SSAs may be characterized in dynamic oscillation modes, using strain and frequency sweeps to measure the viscoelastic characteristics (e.g., storage modulus, G′ and loss modulus, G″). Different SSA, which exhibit significant differences with respect to adhesion can also be discriminated using rheological analysis. Identifying the true viscoelastic properties of the adhesives is critical to understand the adhesion performance of such products. Using the data generated from the rheometer, it is possible to correlate viscoelastic properties to adhesion, and to better understand structure-property relationships.

To understand the rheological characteristics of this material one must identify the linear viscoelastic (LVE) zone by submitting the sample to an oscillatory strain sweep analysis. In the LVE zone, the elastic modulus (G′) and the loss modulus (G″) are independent of the shear strain, indicating that within this strain zone, the response of the material does not depend on the strain applied, and there are no modifications of the material structure. In the LVE zone identification test, the strain is the only parameter which varies, all other parameters, (e.g., temperature and oscillation frequency) are fixed. The LVE graph for the SSA exhibits a large linear viscoelastic zone from 0.5 to 30% logarithmic strain, providing some flexibility to set the strain when performing the frequency sweep at a fixed strain is the next step of the measurement process. Knowing the LVE zone of the material allows one to carry out the second phase of the rheological evaluation, the oscillatory frequency sweep test. Previously unreported data is shown to elucidate this concept in **Figure 13**. Samples were prepared by weighing equal amounts (±2%) of the two parts of the SSA and mixed to ensure homogeneity and then were degassed in a vacuum chamber. The mixed, uncured SSA was coated onto a polytetrafluoroethylene (PTFE) film at a thickness of 0.9 mm, and placed in a forced air oven at a temperature of 130°C for 4 min to cure the SSA. The cured laminate was removed from the oven and allowed to cool to ambient temperature. A second PTFE film was applied using a 6.8 kg (15 lb.) rubber coated roller to ensure complete and consistent contact between SSA and PTFE. The film was allowed to rest for 24 h after which a disc was cut from the SSA laminate using a 24 mm stainless steel punch. Dynamic frequency sweeps (1–100 rad/s) were conducted on SSA with a TA ARES-G2 rheometer at 32°C using 25 mm stainless steel parallel plates and a gap of 0.5 mm with a 10% strain (in the linear viscoelastic region). Data collection was set for 5 pts./decade.

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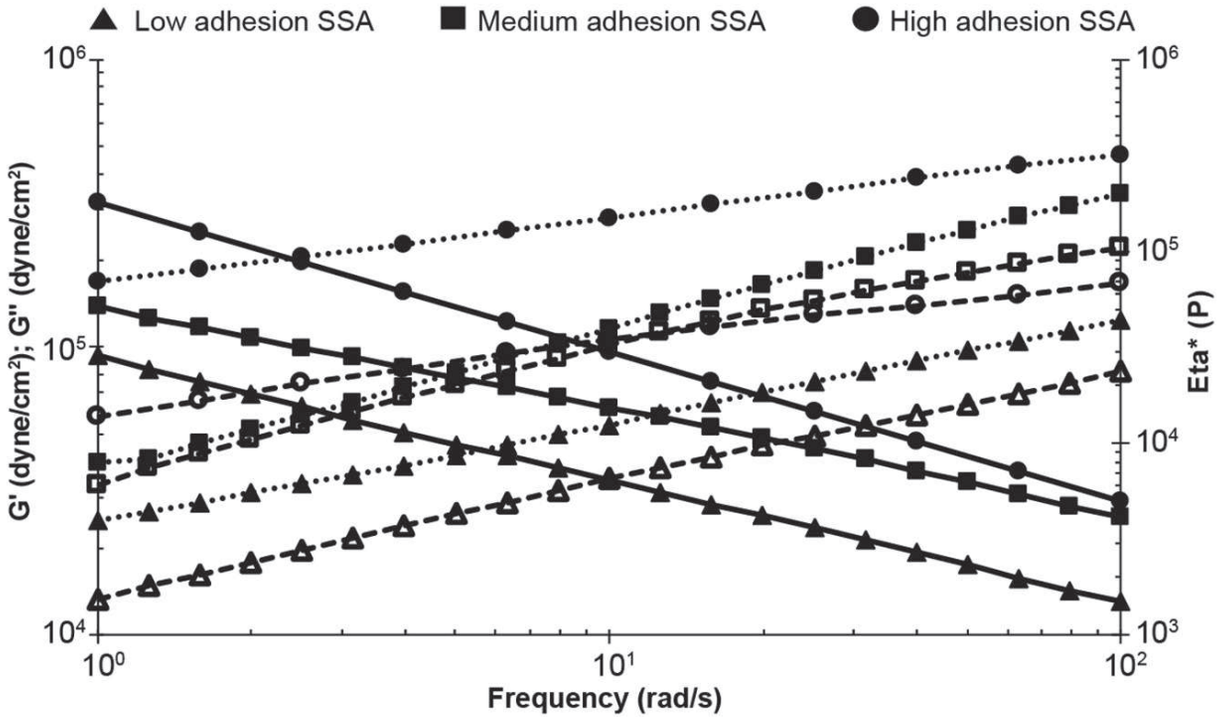


Figure 13. Frequency sweep of three typical SSA.

The frequency sweep test is the most suitable rheological test to assess SSA adhesive properties in the final application. The viscoelastic behavior at low frequencies is related to the bonding step which occurs at low deformation rates and is linked to the SSA ability to wet the surface. Alternatively, the viscoelastic behavior at high frequencies is related to debonding (peel) which occurs at high deformation rates and is linked to the elasticity and energy dissipation during the removal. SSAs with varying adhesive levels can be effectively discriminated based on their rheological profiles. The rheological characterization agrees with the results experienced by skin adhesion, where adhesives with higher G′ and G″ provide higher skin adhesion.

This rheology methodology should be an effective tool and a suitable starting point to understand the structure-property relationships of the SSA technology. It should also provide a means to separate the innate adhesive performance from the influences of substrates. Understanding the relationships between the SSA chemistry, adhesion and rheological profiles will provide key and essential information on structure-property relationships to push the boundaries of SSA even further.

11. Conclusion

Silicone adhesives have been safely and effectively used in a variety of medical applications and are notably present in drug delivery and wound care applications because of the unique benefits and properties provided. Continued investigation has resulted in recent, innovative product developments using established silicone adhesive technologies including innovative

TDDS designs, wound care devices that prevent scar formation and those that are loaded with antimicrobial actives. Adhesive chemistry research has resulted in novel chemistries that combine seemingly incompatible acrylate and silicone adhesive technologies, whereas advances in measurement techniques have brought about clearer understanding of adhesive structure property relationships, avoiding many pitfalls experienced by previous researchers. Despite being used for several decades, the number and variety of recent developments suggest that identifying new medical applications of silicone adhesives remains relevant and the extent to which it may be used has not yet been tapped.

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