Review of silicone adhesives in healthcare applications

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Abstract

This review report provides foundational knowledge of the use, success and challenges of medical silicone adhesives in healthcare applications. Specifically, the authors discuss chemistry, characterization and demonstrated applications of pressure sensitive adhesive (PSA) and soft skin adhesive (SSA) technologies. The authors report factors that should be considered when determining an appropriate adhesive for healthcare applications and discuss recently developed adhesives and considerations for future adhesive developments.

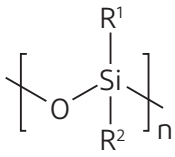
Structure/properties of silicones

First commercialized in 1942 for use as insulating dielectric grease in aircraft ignition systems, silicone-based materials experienced very rapid development in all segments of the industry[1] thanks to their unique physical properties – as masterfully explained by Dr. M.J. Owen in "Why Silicones Behave Funny," successively published in 1981 and 2004[2,3]. The health industry quickly understood the potential of this technology, and it is not surprising that the history of silicones as biomaterials finds its origin with chlorosilane to coat blood-containing devices to delay clotting[4] or with the use of silicone elastomer for duct repair in biliary surgery[5] in 1946.

Since then, silicones have been used in various applications for life improvement and health restoration; they now benefit from more than 70 years of safety and efficacy in medical and pharmaceutical applications, making them a common choice when designing advanced medical and drug systems. This is particularly true when the device is to be attached to the human body for a few hours to several days, requiring reliable yet comfortable adhesion to skin. In wound care and transdermal drug delivery systems, medical silicone skin adhesives have demonstrated their efficacy in providing both atraumatic adhesion and optimal drug diffusion. The emerging trends toward remote patient monitoring to anticipate health issues and allow return-to-home care with confidence and prevent rehospitalization have positively fueled the demands for wearable and connected medical devices that patients can wear discreetly and securely for a couple of weeks, as well as easily change or reposition when required. Again, silicone technology is well-positioned to provide suitable adhesive solutions by building on its recognized suitability in well-established medical applications and extending its performance to answer the new challenges rising from the development of advanced e-health systems.

The term "silicone" normally refers to a chemical structure based on the siloxane unit as shown in Figure 1, with the substituent R being mainly an alkyl group or another siloxane sequence. The substitution also can be designed to be a reactive functionality (e.g., H, OH, vinyl, alkoxy, etc.) or to deliver specific properties, such as surfactant with polyether chain or anchorage with glycidyl or amine group.

Figure 1. Typical dimethyl siloxane unit; R^1, R^2 are alkyl groups



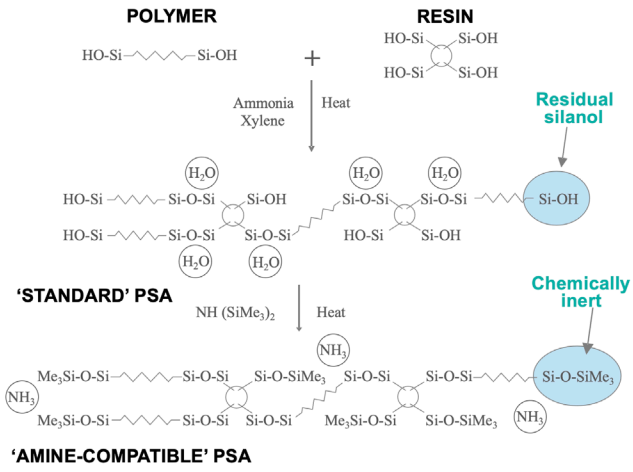
The most commercially available molecular sequence is the polydimethylsiloxane structure, commonly adopted for economic reasons – and because it delivers the optimal interfacial properties, which are the *raison d'être* of silicones. Regarding their uses as adhesives, the dimethylsiloxane architecture is directly responsible for the bulk viscoelasticity and the surface activity that are the key physical parameters allowing a material to both adhere to a substrate and be removed from it. Associated with the confirmed biocompatibility, silicone technology allows for designing different types of pressure sensitive adhesives to answer the demanding needs of medical applications for temporarily attaching and securing therapeutic devices to the body.

Pressure sensitive adhesives (PSAs) differ from structural adhesives in that the adhesive-substrate interface does not resist separation when the adhesive is peeled off. In other words, PSAs are intended to show adhesive failure – especially when skin is the substrate – whereas this would be considered a major flaw for cement and glue. Silicone material can be designed and formulated to be pressure sensitive adhesives (e.g., sticking plaster, adhesive bandage) and/or structural adhesives (e.g., sealant, surgical glue).[6]

Silicone pressure sensitive adhesives (PSAs)

Silicone PSAs are viscoelastic compounds based on the resin-in-polymer concept. Unlike organic PSAs, they do not need additives such as antioxidants, stabilizers, plasticizers, catalysts or other potentially extractable substances. They are produced by condensing silanol end-blocked polymer with a silicate resin in the presence of ammonia, as shown in Figure 2. The polymer is a medium-viscosity to low-viscosity silanol end-blocked polydimethylsiloxane. The resin is a three-dimensional silicate network. Ammonia initiates the crosslinking reaction, resulting in a reinforced siloxane network with improved cohesive strength.

Figure 2. Silicone PSA schematic



Standard silicone PSAs contain a certain level of silanol functionality that can favorably participate in the compatibilization of drugs and excipients. However, these reactive hydroxyl groups could further react with amine-containing drugs, thus impacting adhesive performance and potentially drug release rates. For this reason, a second family of adhesives is produced by further reacting the adhesive with a trimethylsilyl endcapping agent. This family is referred to as amine-compatible and exhibits enhanced chemical stability, especially in the presence of amine-functional drugs. Silicone PSAs produced by this process have been shown to have many key features that make them suitable for applications bonding to skin.

A subfamily of standard PSAs referred as "standard reduced silanol" (SRS) was developed to offer a lower level of silanol groups. These PSAs still are classified as standard PSAs from a regulatory point of view. The reduced residual silanol level in SRS BIO-PSAs is achieved by using a less-reactive resin for the silanol condensation reaction. The use of a less-reactive resin leads to "softer" adhesives with:

- Less silanol condensation
- Lower complex viscosity (i.e., eta star (η^*))
- Lower viscosity

The adhesive performance of silicone PSAs is based on the viscoelastic behavior as demonstrated by their rheological profiles, ensuring a good balance of wetting and spreadability (viscous component) brought by the silanol polydimethylsiloxane and cohesiveness (elastic component) brought by the resin.

The two most important factors in determining the performance characteristics of silicone PSAs are the resin-to-polymer ratio and the degree of crosslinking[7]. A certain amount of resin is required to tackify the polymer so that it exhibits PSA qualities. Above the minimum level, increased resin content results in a more tightly crosslinked silicone network and more cohesive strength (or shear strength). More fluid leads to higher tackiness, softness and adhesion to skin as the PSA flows and more readily conforms to the skin surface.

In each family (standard or amine-compatible), silicone PSAs are proposed with three different ratios of resin-to-polymer, respectively:

- Low tack and high cohesion
- Balanced tack/cohesion
- High tack

Silicone PSAs are available in different processing solvents, mainly ethyl acetate or heptane. The solvent is selected according to the final patch formulation strategy, (e.g., selecting a solvent in which all formulation components may be homogenized during the coating step). Solventless varieties of silicone PSAs also are available and may be processed using standard hot-melt coating equipment.

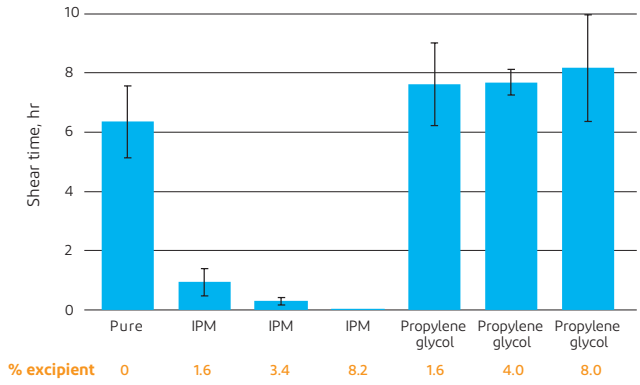
Characterization of PSAs

PSA characterization is critical to product development and quality control. Physical performance property testing – sometimes referred to as "tape tests" and "peel tests" – often is conducted. Common properties assessed by tape testing include adhesion, shear strength, tackiness and the force required to remove the release liner from the adhesive. This type of testing is not limited to healthcare applications, and many of the tests for healthcare adhesives were derived from similar tests for the broader adhesive market. Tape testing typically is performed by casting or coating the adhesive onto a substrate in a specified thickness – essentially creating a tape – and then measuring properties of the created tape. Silicone PSA testing typically is conducted on relatively thin adhesive layers, commonly between 2 to 5 mil (approximately 51 to 127 micron). Adhesive peel tests are well-described in the literature and are common to most adhesives; they typically occur at 90° or 180°, and the force to remove the adhesive from a substrate (e.g., stainless steel in many cases) is measured. The advantages of tape testing methodology include ease of setup, reproducibility and a straightforward interpretation of data. Unfortunately, these tests often have a high degree of variability, resulting in wide specification limits and poor correlation between users, and thus limited prediction of the adhesive's performance in real-life applications. Tape test results may be influenced heavily by adhesive coating thickness, the substrate onto which the adhesive is coated and the substrate against which the PSA's adhesion is measured. To minimize these influences, there must be accurate control of sample preparation, including adhesive thickness, standardization of tape materials (e.g., backing and release liner) and test parameters. Despite these drawbacks, tape testing is nearly ubiquitous amongst adhesive manufacturers and users.

A distinction between peel adhesion and the tack of an adhesive should be made; peel adhesion is representative of the bonding strength of an adhesive, whereas tack is representative of the ability to quickly stick to a substrate. Analytically, 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 immediately after the adhesive contacts the test substrate, whereas peel adhesion is measured after the adhesive is left in contact with the substrate for a longer period. A longer dwell time between application and testing allows the adhesive to wet out on the surface and the adhesion to build.

Due to the influence of substrates on adhesion and tack, the shear test may have more direct relevance to skin contact adhesive applications than peel adhesion and tack tests. Typically, the static shear test is the measurement of the time for the adhesive to detach from a surface (e.g., stainless steel) under a constant weight and is indicative of the cohesive strength of an adhesive. Shear tests of fully formulated adhesive matrices may be conducted to evaluate how additives (e.g., drugs and other materials used to solubilize and enhance drug permeation) impact the shear strength of a transdermal drug formulation. By way of example, as shown in Figure 3, the addition of different levels of propylene glycol does not have a statistical impact on the static shear of a low-resin-content silicone PSA. However, a significant decrease of the static shear was observed with the addition of isopropyl myristate, demonstrating how different materials can impact the cohesiveness of the adhesive matrix.

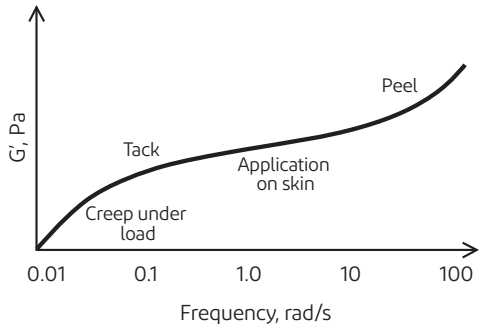
Figure 3. Impact of the addition of different levels of isopropyl myristate (IPM), propylene glycol on the static shear of a low-resin-content silicone PSA



Tape properties may predict how quickly a system bonds to a substrate and how much force is needed to remove it. However, those tests do not measure the wear performance of the system. To better understand and predict the wear performance of adhesive systems, rheology often is used to understand the adhesive bulk viscoelastic behavior. 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 may predict wear performance of PSAs. As shown in Figure 4, a generalized rheological curve can be correlated to common tape properties[8,9,10,11].

Figure 4. Schematic representation of the link between rheological profile and PSA wear performance

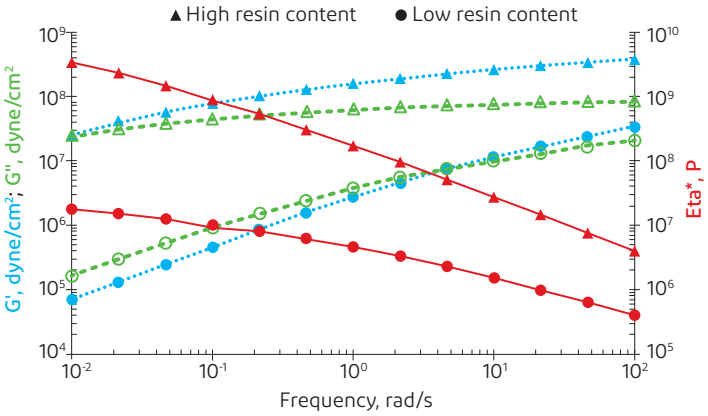


For viscoelastic materials, such as silicone PSAs, the frequency sweep curves are sensitive to structural differences (e.g., crosslink density) and formulation changes (e.g., resin-to-polymer ratio). This sensitivity provides a means to identify, characterize and predict adhesive wear performance.

The storage modulus (G') is an indicator of how elastic the adhesive is and how much energy is stored during deformation. The loss modulus (G") is an indicator of viscous component of the PSA and how much energy is lost as heat. The complex viscosity (η^*) is an indicator of the adhesive bulk viscosity and can be related to cold flow of the adhesive. Bonding of an adhesive system is dependent on the wetting behavior of the adhesive when it encounters skin and occurs at a low deformation rate. Rheologically, the storage modulus (G') values at low frequency are 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. Rheologically, the storage modulus (G') and loss modulus (G") at high frequency may be related to the peel adhesion and tack (i.e., quick stick) properties of an adhesive. For bonding, the viscous contribution should be higher than the elastic contribution to the PSA's viscoelastic profile. In rheological terms, it means that at low frequencies, G' should be less than G" – and the opposite for the debonding step, represented at high frequencies, where G' should be greater than or equal to G". Based on those interpretations, the rheological traces in Figure 5 suggest that the increase of resin content should lead to a reduction of adhesive cold flow (i.e., an increase of the complex viscosity with resin content) and an increase of the adhesion level (i.e., an increase of both G' and G" with resin content).

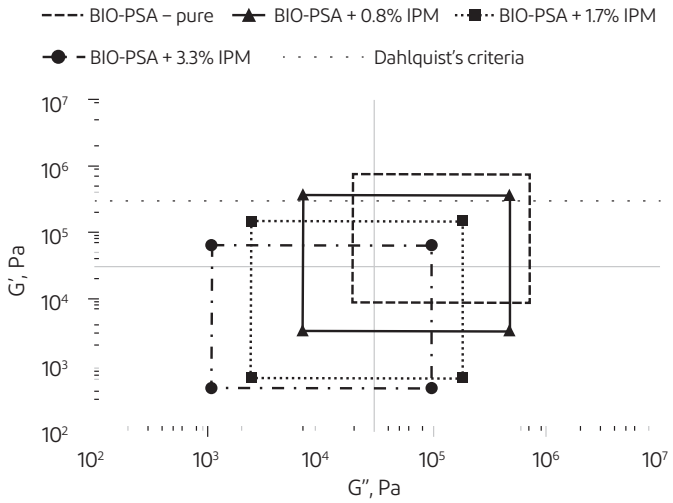
*Figure 5. Typical frequency sweeps of silicone PSAs at two common resin contents (**high**, 8 mm parallel plates, 0.35% strain; **low**, 25 mm plates, 0.5%); all samples tested at 30°C and 1.5 mm gap*



In 1969, Carl Dahlquist defined a specific elastic modulus point below which a material will have quick tack regardless of other parameters. In the early 1990s, E.P. Chang developed a theory to interpret rheological data of PSAs and establish criteria for PSA classification when used in conjunction with the Dahlquist criteria. This theory is now well-known and used as the "Chang viscoelastic window." As shown in Figure 6, a G′ versus G" graph is divided into 4 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 upper-right quadrant corresponds to high modulus and high dissipation. Therefore, materials in this quadrant with characteristic high G′ modulus compensated by the high G" are anticipated to be adhesive materials with high adhesion but low tack and high shear resistance. Conversely, the lower-left quadrant corresponds to low modulus and low dissipation. For these materials, peel values usually are low because of the comparatively low debonding cohesive strength and low dissipation.

The lowermost edge of the window, which is linked to bonding of the adhesive, is far below Dahlquist's criteria, so the adhesive can be expected to have reasonable tack. Changes in the Chang viscoelastic window of a low-resin-content (high-tack) silicone PSA can be observed as isopropyl myristate (IPM) – a commonly used permeation enhancer that can plasticize or soften the adhesive – is added. As illustrated in Figure 6, the Chang viscoelastic window moves from the upper-right quadrant for the neat adhesive to the lower-left quadrant as more IPM is added and the adhesive softens. There is a significant shift in the position of the upper-right corner as IPM content increases. This shift is linked to debonding (peel) efficiency, suggesting that an increase in IPM content decreases peel efficiency. Adhesives with poor peel efficiency may remove less cleanly from surfaces to which they have bonded. Finally, the window size increase indicates a decrease of PSA shear strength that likely is due to better solvent compatibility in the PSA. These data support known observed changes in adhesive properties as plasticizing agents like IPM are added and support the further use of rheological measurements to characterize changes in PSA wear properties.

Figure 6. Chang viscoelastic window concept adapted for low-resin-content silicone PSA with differing amounts of IPM versus neat adhesive

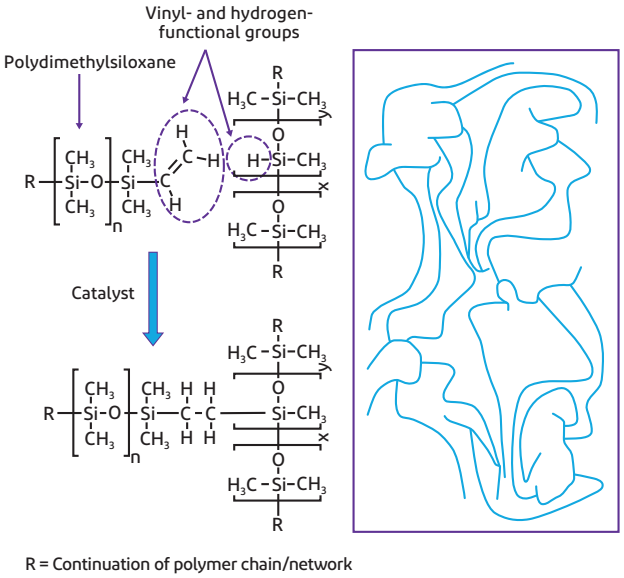


Soft skin adhesives (SSAs)

Silicone tacky gel technology was introduced to the wound care market and named "soft skin adhesives" (SSAs) by Dow Corning Corporation in the 1990s. Similar materials are offered today under a variety of brand names from many silicone suppliers. In a segment historically dominated by acrylic adhesives, the tacky gel technology concept disrupted the industry by securing wound dressings while providing gentle adhesion upon removal. Due to their reliable adhesiveness while being easier to remove and causing less pain upon removal than many other adhesive technologies, SSAs have become the material of choice in many advanced wound care and scar therapy applications.

The elastomeric structure of SSAs is obtained by crosslinking a network of polydimethylsiloxane (PDMS). The reaction is based on an addition reaction (hydrosilylation) between vinyl-functional PDMS (polymer) and hydrogen-functional siloxanes (crosslinker) as shown in Figure 7. The cure reaction is catalyzed by a platinum complex, which can occur at room temperature or be accelerated at elevated temperature (80°C to 145°C) without the formation of reaction by-products. As crosslinked, thermoset materials, SSAs have a low susceptibility to cold flow and plasticizing effects. SSAs are supplied as two-part systems with the catalyst in one part and the crosslinker in the other. The materials characteristically are transparent before and after curing into a solid matrix[6,12].

Figure 7. A proposed schematic for the hydrosilylation reaction



SSAs are based on a polydimethylsiloxane network that 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 – which build adhesiveness on a viscous phase bodied with a silicate resin – SSAs are based on silicone elastomer technology modified to deliver the relevant viscoelastic 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, SSAs have a similar texture and feel to other gels; however, SSAs are not typical polymeric gels because they are not based on an insoluble polymer network swollen with fluids. The viscoelastic 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.

The adhesive property of SSAs is based on the capacity of the elastomer surface to quickly wet the skin and conform to skin irregularities without the additional compression step required for a PSA. 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 experience very limited flow, and they consequently have little ability to pick up materials from the surface of the skin. Therefore – unlike silicone PSAs – the adhesive surface of SSAs remains relatively clean upon removal from the skin, which allows for removal and easy reapplication of the dressing or device to the skin and makes repositioning possible.

The SSA technology has been used extensively in scar treatment and advanced wound management, demonstrating safety and efficacy recognized by wound care professionals. SSAs may be recommended for use in designing medical adhesive devices, tapes, bandages, drapes and wound dressings. They have been noted for many benefits, including high tack for quick bonding to skin, permeability to moisture and gases (e.g., CO_2, O_2), reliable adhesiveness and cohesiveness, gentle adhesion to fragile and compromised skin, no skin-stripping, and pain-free device removal[6,12].

Substrate selection is important when designing an adhesive device based on SSA, as the nature of the substrate can have a significant impact on the coating and cure conditions during the manufacturing phase. Anchorage of the adhesive to the substrate, cohesiveness of the adhesive after cure and the ultimate wear behavior of the device when applied to the body all can be impacted by substrate selection.

SSAs typically are processed by mixing the two parts and coating the mixture directly onto the final substrate (e.g., backing film), with the 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 it often ranges between 150 g/m² and 250 g/m². The curing phase typically is completed at an elevated temperature that is adjusted to the temperature sensitivity of the substrate. After cooling, the adhesive surface is protected by a release liner that is peeled off when the end-user applies the adhesive to skin. The choice of release liner is a critical factor, as it can affect the device stability and make it unusable if the protective film cannot be removed easily 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 lockup effect upon storage. However, uncoated polyethylene films – especially low-density polyethylene (LDPE) grade – can provide an acceptably low and reasonably consistent release force from the SSA[13,12].

Relevant markets & uses

Transdermal drug delivery systems (TDDS) are suitable alternatives to oral dosage forms to overcome the very low bioavailability encountered with some molecules, such as rotigotine. The adhesive is a critical component of a TDDS – both as reservoir matrix and delivery vector of the drug. A judicious selection of the appropriate adhesive is an important consideration for the development of a new TDDS for optimizing skin penetration and wear properties. The adhesive must be compatible with the drug and the other excipients, as well as with the variability of patient skin. Finally, it is critical that the adhesive provides acceptable release of the drug and favors its partitioning into the skin.

Silicone PSAs have been used in TDDS for more than 40 years. They were introduced in this use in 1981 in a nitroglycerine reservoir patch for the treatment of angina pectoris. Since then, many patch products using silicone PSAs – either as the primary adhesive system or in combination with acrylic adhesives in multilayer designs – have gained approval. Multiple designs are reported in the literature and are available commercially, including reservoir, matrix and drug-in-adhesive systems. Examples of active pharmaceutical ingredients (APIs) used in commercial TDDS are fentanyl for pain management, estradiol for hormone replacement therapy, and rotigotine or rivastigmine for CNS diseases[12].

During the last 30-plus years, multiple fentanyl patches have been formulated with silicone PSAs. The first fentanyl patch was introduced to the U.S. market in 1991. In general, fentanyl patches containing silicone PSAs have the highest drug depletion and lowest residual drug content after the 72-hour wear period compared to patches containing polyisobutylene (PIB) or acrylic PSAs.

A rotigotine transdermal system called NEUPRO® was developed and approved for idiopathic Parkinson's disease and restless legs syndrome in the U.S. and European Union. This transdermal delivery system consists of a thin, silicone-based, matrix-type patch with a 24-hour wear period[14].

Recently, Puri at al. reported the development of a TDDS for tenofovir alafenamide – a potent drug of tenofovir – for human immunodeficiency virus (HIV) prophylaxis and HIV and hepatitis B virus treatment. The silicone-based patch showed the highest permeation compared to PIB-based and acrylates-based patches[15].

New SSA technologies have been developed that can achieve higher adhesion, longer wear times and improved drug compatibility to address emerging medical market trends, including wearable devices and topical drug delivery patches[6]. The use of SSA technology to formulate drug delivery matrices enables drug delivery system designs that address the need 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 APIs have been studied, including those indicated for pain relief and local anesthesia, antibiotics, and dermatological actives[13]. Wound care products that utilize silicone tacky gels as the skin contact adhesive and are loaded with chlorhexidine gluconate and other antimicrobial agents have been investigated and commercialized[16,17]. 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 historically has been used.

New silicone adhesive developments

Performance-enhancing advancements have been realized for both PSAs and tacky gels, enabling their utility in more-demanding applications. Hybrid PSAs that combine silicone and organic functionalities promise expansion in healthcare applications, enhancing drug solubility and enabling treatment options for drugs and indications not available with previous adhesive chemistries. One of the most advanced systems has been silicone-acrylic PSA technology, either as blend or copolymer[18,19,20,21]. Unlike simple blends, the copolymer-based adhesives are capable of much finer domain sizes and demonstrate superior phase stability during formulation and in cast films. Other hybrid adhesive developments promise increased hydrophilicity, allowing straightforward incorporation of hydrophilic drugs and improved wearability on moist skin, with similar adhesion to traditional PSA while utilizing less-specialized release liners.

To tackle new market trends in terms of adhesives for advanced medical systems such as wearable devices and topical drug delivery patches, new SSA technology has been adapted and customized to allow more effective processability and to achieve higher adhesion and longer wear times of final products[22,23,24,25]. These advancements have been accomplished through the use of various silicone polymer chain lengths (i.e., molecular weight), differing functionalities and reinforcement of the open three-dimensional structure. While it is unknown exactly which needs or applications will materialize, silicone adhesives have a proven history of alterations to meet market challenges and increasingly demanding needs, and applications requiring increased electrical conductivity and hydrophilicity may be on the horizon. ■

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