Recent developments in silicones for topical and transdermal drug delivery

Silicones have been used in medicines, cosmetics and medical devices for over 60 years. Polydimethylsiloxanes are polymers that are typically used either as an active in oral drug products or as excipients in topical and transdermal drug products. Inherent characteristics like hydrophobicity, adhesion and aesthetics allow silicones to offer function and performance to drug products. Recent technologies like swollen crosslinked silicone elastomer blend networks, sugar siloxanes, amphiphilic resin linear polymers and silicone hybrid pressure sensitive adhesives promise potential performance advantages and improved drug delivery efficacy. This article presents a review of recent silicone material developments focusing on their function as excipients influencing drug delivery in topical and transdermal systems.

Development of controlled release drug delivery systems requires simultaneous consideration of numerous interdependent factors, including the drug's physiochemical properties, route of administration, nature of delivery vehicle, mechanism of drug release, ability to target and biocompatibility of the product [1]. This presents major challenges for designing and developing a controlled release dosage form specific to the delivery route of administration, for instance, oral or dermal drug delivery. The **active pharmaceutical ingredient** (drug) often gets most of the attention when it comes to a drug product, although the **excipients** or nondrug components of a formulation also play a crucial role in delivering the active in each dosage form.

Drug delivery via skin is an attractive alternative to oral and hypodermal delivery, as it eliminates first pass metabolism and drug degradation in the GI tract [2] encountered by oral administration; and is relatively painless, and easy to use, in contrast to hypodermic needles [3,4]. However, it is known that the stratum corneum represents a major permeability barrier [5]. The anatomy of skin is such that the lipid bilayers are perfectly stacked to exclude foreign substances [6]. Strategies including, disrupting the lipid bilayer by

using permeation enhancers, shifting the partitioning of the drug from the vehicle to skin and delivering additional solvent leading to higher convective transport of molecules or enhancement of drug solubility, have been utilized successfully to overcome the barrier to deliver the drug to or across the skin [5].

A topical/transdermal formulation typically contains 90% or more excipients; inactive ingredients which are included to perform different functions in the product. Penetration and permeation of the drug through the skin is not only dependent on the physiochemical nature of the drug but also on the formulation composition, that may alter the properties of the skin and hence influence the permeation of the drug [7]. In topical formulations, polymeric materials generally provide the base or matrix for the final dosage form, but can also impact drug delivery. Since different drugs interact differently with different polymers and affect the release properties differently [8–10], individual polymers or polymer mixtures have historically been used to modulate drug release properties. The influence of minute changes in the chemical structure, the amorphous or crystalline state, hydrophobic or hydrophilic nature of the polymers, on drug release char-

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Key terms

Active pharmaceutical ingredient: The ingredient in a pharmaceutical drug product responsible for the claimed therapeutic benefit. Often the term is interchangeably used with 'drug' and 'active'.

Excipient: Any ingredient in a pharmaceutical drug product excluding the drug.

Pressure sensitive adhesive: A polymeric material which provides adhesion between two surfaces upon applying pressure. A pressure sensitive adhesive in the transdermal drug delivery system provides the adhesion between skin and the patch for the intended period.

Transdermal drug delivery system: This often refers to the transdermal drug delivery using a patch system. The patch is applied on the undamaged skin surface and the drug is delivered from the patch to the systemic circulation.

acteristics has also been demonstrated [10–14]. Topical formulations use a variety of polymeric materials as matrices including petrolatum, acrylic polymers, cellulose derivatives, chitosan, carageenan and silicones [15]. In transdermal patch formulations, the polymeric **pressure sensitive adhesive** (PSA) material is a key component, creating a bond between skin and product and impacting all other performance criteria [16]. Three PSA chemistries are commonly used in transdermal products, namely acrylic, silicone and synthetic or natural rubber [16].

Silicones are synthetic polymers containing Si–O siloxane bonds. The most common silicone polymers are polydimethylsiloxanes (PDMS), the chemical structure of which is shown in [Figure 1](#). The unique characteristics of PDMS such as low intermolecular forces between pendant methyl groups, compact size of methyl groups, high-siloxane backbone flexibility, high-siloxane bond energy and partial ionic nature of the siloxane bond account for their applications differentiated from either organic or inorganic polymers. [17]. The multitude of physical forms and the physiochemical properties that silicones can display has led to their adoption in a diverse array of healthcare applications. The silicone chemistry is known and has been well documented. Interested readers can refer these text books for more details [18–20].

Although a variety of silicone forms and chemistries have been used in medicines, cosmetics and medical devices for over 60 years, monographs only exist for two materials as excipients [21], cyclomethicone and dimethicone. Silicones can be found in the formulations of more than 350 registered drug products as actives or excipients [22]. The use of silicones has been continuously increasing. For instance, a search in US National Library of Medicine for dimethicone and simethicone (both as an active) produced 845 and 282 results [23]. From a regulatory perspective, it is

therefore relatively easy to use these two ingredients in pharmaceutical applications. However, at times, a formulation or product form requires performance characteristics that may not be possible using only compendial excipients. When noncompendial excipients are selected, the regulatory burden for the formulation can be much greater. Still, several noncompendial silicone excipients exist in current commercial pharmaceutical products to fulfill the performance requirements such as to carry or solubilize actives, to improve aesthetic properties in topical therapeutic formulations and as adhesive matrices in transdermal drug delivery patches.

This review describes recent advances in the application of silicone polymers in topical and transdermal drug delivery via skin and focuses on work reported in the literature in approximately the last 10 years. Several types of organic polymers, both natural and synthetic, are used in topical/**transdermal drug delivery systems** and are discussed in several review articles [24–27]. Often, the review articles include commercially used silicones as well in the discussion along with the other polymers. This particular manuscript specifically focuses on silicone's utilization in the recent years in the topical/transdermal drug delivery area. It also provides emphasis on the advantages associated with silicones when used in these drug delivery technologies. Additionally, not-yet-commercialized newer silicone developmental technologies which demonstrated potential benefits in topical/transdermal drug delivery have also been reported in this manuscript. The authors found a greater number of references available in the patent literature compared with peer-reviewed journal articles, which are summarized here rather than reviewing each and every publication. For the readers' convenience, the 'topical drug delivery' section refers to drug delivery to and across the skin by the topical liquid or semisolid formulations.

Silicones in topical drug delivery

The use of silicone materials in many topical products has been reported [22]. Two of the most widely used topically applied silicones in pharmaceutical applications are compendial excipients – specifically dimethicone and cyclomethicone, because of their unique properties like skin protectancy, emolliency and low surface tension [28–30]. In spite of its highly hydrophobic nature, several types of silicone materials have been successfully incorporated in water-based products as emulsions. While the cosmetic industry benefited hugely, silicones have made an impressive contribution to pharmaceutical drug delivery applications as well. However, other, noncompendial excipients are also used in topical pharmaceutical applications. A recent estimate is that over 50% of current skin care products contain at least one silicone material [21].

The silicones used in these applications are generally recognized as safe and are known for having a variety of aesthetics that are preferred by consumers. Specific property improvements noted in silicone-containing formulations include ease of spreading, less tackiness and a silkier, 'elegant' and more lubricious feel than comparable formulations without silicones [21,31,32].

The complexity of the numerous dermatologic reaction patterns fall under the heading of sensitive skin. Approximately 40% of population believes it possesses the characteristics of sensitive skin creating a sizable demand for products designed to minimize skin sensitivity. Sensitive skin can be defined in both subjective and objective terms and the latter may include skin responses like allergic contact dermatitis [33]. Though considered generally safe, investigations on individual silicones have been carried out for skin sensitivity, however, not focused only on skin response like allergic contact dermatitis. A final report by the cosmetic ingredient review expert panel provides skin irritation and sensitization by several individual silicones [34].

The impact of patient nonadherence on treatment failure is an area of increasing concern and poor aesthetics may be a contributing factor to purposeful patient nonadherence with medical treatment regimes. Because of its chronic nature and historical reliance on topical medications, psoriasis is a condition on which the dermatology community has focused to understand the causes of patient nonadherence to the treatment regime. It has been reported that more than a third of psoriatic patients are not compliant with their prescribed medication [35] despite the well-documented link between adherence to a treatment regime and successful clinical outcomes [36]. While patients expressed frustration with the (lack of) treatment efficacy, research has suggested that vehicle-related factors were ranked as 'important' to patients when considering their motivations for intentional nonadherence to their treatment regimes [37]. Among the vehicle-related factors determining intentional nonadherence rates were aesthetic reasons such as 'the medication felt unpleasant' and the time-consuming nature of application [37]. Dosing frequency (once- vs twice-daily application) which is sometimes suggested as having an impact on patient compliance was not a determining factor in patient adherence to a treatment regime [37].

In addition to the aesthetic improvements that silicones may provide to a topical formulation, other more objectively measured properties can also be provided. **Substantivity** is a term describing the adherent qualities of a topical formulation and its ability to be retained on the skin over time [38]. Silicone gums are very-high-molecular-weight PDMS polymers with a viscosity in excess of 100,000 cP, and while still liquid by definition, they are no longer pourable, and can hold a shape for

Figure 1. Chemical structures of polydimethylsiloxane.

a short time. These silicone gums are highly substantive on the skin and have been shown to significantly improve the substantivity of an active [39]. A pharmaceutical product's resistance to washing off and rubbing off may lead to more prolonged exposure of the drug on the skin surface, which in turn may lead to a greater amount of drug being available, and ultimately crossing the stratum corneum barrier. One study demonstrated that 25% of the silicone gum (in hexamethyldisiloxane, a volatile silicone carrier fluid) applied to the forearm skin surface, remained after 8 h of daily activities [40]. Consistent with the substantivity of the gum, detectable levels of the drug ketoprofen were observed 6 h after application, as compared with 40 min in a comparative formulation without the silicone gum [40]. Skin hydration via occlusion can also temporarily alter the barrier properties of the stratum corneum to allow for an enhanced flux of both hydrophilic and hydrophobic drugs. Most polydimethylsiloxanes are nonocclusive, but silicone gums as well as organic modified silicones (e.g., alkylmethylsiloxanes) are somewhat occlusive [41], and so are known to reduce transepidermal water loss and therefore hydrate the epidermis. As described, silicones can impact physiochemical properties of a formulation, such as substantivity and **occlusivity**, which can impact the efficacy of a drug formulation. The aesthetic properties of silicones may also impact the final properties of a formulation and thereby the treatment regimen.

New silicone technologies for efficient drug delivery

Advancement in the development of innovative technologies and materials offer new avenues of topical drug delivery applications by silicones. Given the wide variety of silicone forms and applications, it is difficult to foresee which, if any, of the current materials may find util-

Key terms

Occlusivity: The ability of a formulation ingredient(s) in the formation of a layer/coating/film on the skin surface which assists for the prevention of the loss of water from the skin surface.

Substantivity: The ability of a formulation ingredient(s) in the formation and adherence of a layer/film on the skin surface which resists easy wash-off or rub-off of the layer so that the layer may help to retain the drug incorporated in it for a longer period.

ity in approved topically applied pharmaceutical products. The investigation for well-differentiated or novel applications is always progressing by both academia and industry not only utilizing the inherent aesthetic characteristics of silicones but also seeking enhanced therapeutic efficacy of the drug product. Current uses in other life science-related industries, a demonstrated advantage of use at the research level and intellectual property protection filed, suggest a great potential for several silicone technologies and materials for the topical drug delivery arena. Detailed below are some technologies and materials that have been recently reported and relate to topical pharmaceutical drug delivery applications.

Silicone elastomer blends are slightly crosslinked, 3D network polymers are swollen in an organic or silicone solvent to create a gel. The general procedure to prepare the gels includes a platinum-catalyzed hydrosilylation reaction of Si-H functional silicone in presence of the solvent followed by shearing the gels into discrete particles [42,43].

These semi-solid silicone materials have been utilized to make nonaqueous, topically applied formulation to efficiently deliver drugs. Forbes *et al.* reported efficient *in vivo* delivery of antiretroviral HIV drug, maraviroc, to rhesus macaques from a nonaqueous silicone elastomer gel formulation over nonsilicone-based formulation(s) pertinent to a microbicide delivery system (see Figure 2) [44]. The silicone formulation also demonstrated no irritation to mucosal tissue and enhanced mucosal retention for efficiency. Subsequently, the same research team using a different silicone elastomer gel that was partially modified with relatively hydrophilic silanol-terminated PDMS reported enhanced release of maraviroc and emtricitabine (another antiretroviral HIV drug) over 24 h and less cytotoxicity compared with standard hydroxyethylcellulose gels [45]. The nonaqueous, silicone gels may offer several advantages over more conventional water-based gels for vaginal delivery systems, including better formulation of poorly water-soluble active compounds, prolonged pharmacokinetic profiles and greater stability of hydrolytically vulnerable compounds.

While the above research reports the drug release to vaginal mucosal tissues, where the stratum corneum barrier does not exist, another work reported by Aliyar *et al.* demonstrated efficient *in vitro* delivery of ibuprofen across human cadaver skin using silicone elastomer gel-based formulation compared with a commercial product and similar formulations made of nonsilicone chemistries [46]. The increased efficiency

was also demonstrated against the commercial product *in vivo* using rats (see Figure 3).

Utilization of silicone elastomer gels in a variety of drug delivery applications has been reported via granted and or sought intellectual property publications. Notable references include formulations or compositions to deliver actives like ingenol angelate [47], retinoic acid derivatives [48], amino acids [49], antiperspirants [50], clobetasol propionate [51] and several other actives [52,53]. Crosslinked silicone matrix-type polymers were reported for the encapsulation and subsequent delivery of actives for improved stability and performance [54] and in some instances to deliver protein [55,56]. Using different types of silicone elastomer gels, dual drug delivery, delivery of hydrophilic and hydrophobic drugs from gel formulations has also been reported [57].

Delivery of actives by soft skin adhesive

Soft skin adhesive technology has revolutionized the wound care industry with its unique skin-friendly adhesion characteristics. Like the gels described above, this technology also utilizes a platinum-catalyzed hydrosilylation crosslinking reaction. However, the resulting product is a tacky, cohesive matrix rather than a dispersed gel. This technology has been utilized to deliver antimicrobial actives for wound therapy [58]. The loosely crosslinked structure has proven its suitability for topical drug delivery as well. The patches made from soft skin adhesive showed noteworthy 24-h cumulative release of 45 to 58% estradiol compared with 1 to 12% by other silicone polymers over the same period of 24 h [59].

Emulsions

The possibility of delivering both lipophilic and hydrophilic drugs topically has been disclosed using emulsions formed by a soft silicone elastomer and a hydrophilic polymer like polyvinyl alcohol [60,61] or polyvinyl pyrrolidone [62]. Depending on the ratio of silicone to the other polymer, the emulsions provided films of varying appearance from glossy to matte, and colored from white to transparent, with varying mechanical properties. These differences may in turn alter the drug delivery profile too. Silicone-containing emulsion compositions were reported to deliver several actives including niacinamide [63], thiazolium compounds [64], chlorhexidine [65] topically. A stable three-phase emulsion comprising an aqueous gel outer phase and a water-in-silicone oil inner phase has been described for the topical delivery of pharmaceuticals [66]. A variety of silicones in different amounts may be incorporated into the water-in-oil phase of the three-phase emulsion to prepare emulsions with different characteristics. Emulsions made of high molecular weight uncrosslinked

Key term

Topical delivery: Delivery of a drug into the (dermal) skin.

PDMS (silicone gum) [67] or PSAs using polymeric surfactant like ethylene oxide-propylene oxide block copolymer [68], have also been demonstrated utility in topical drug delivery applications.

Film, foam & spray dosage forms

Topical dosage forms, which provide a film on top of the skin, offer advantages like, longer dosage retention, occlusivity, rub-off resistance and barrier properties all of which influence drug delivery. Several novel silicone-containing film formers have been investigated for utility in topical drug delivery. Compositions containing a silicone acrylate hybrid polymer [69], sugar siloxanes [70,71] and amphiphilic resin-linear organosiloxane block copolymers, which may improve the solubility of hydrophilic actives into the siloxane matrix [72], have also been investigated for topical drug delivery.

Low molecular weight volatile silicones like hexamethyldisiloxane have been utilized in many topical spray formulation dosages to deliver the drug. These volatile silicones provide functional properties like nonirritation [73], moisture maintenance and solubilization of the active [74]. Literature suggests that actives like vitamin-A, diclofenac and lidocaine have been investigated in spray formulations. The volatility of the silicone in these applications helps increase the drug concentration in the formulation quickly to saturation thereby assisting efficient drug delivery [75,76]. Silicones have also been reported for topical foam dosage forms [32,77–81].

The exploration of the use of novel silicone technologies in topical drug delivery is quite impressive as observed in the literature as described above, particularly in the patent arena. Though dimethicone and cyclomethicone have been utilized in numerous topical drug products, the use of other silicone materials as a primary polymer in topical pharmaceutical formulations is infrequent, whereas other nonsilicone polymers like petrolatum, carbomer (acrylic polymer), cellulose derivatives, poly(ethylene glycol), poly(ethylene glycol)-co-poly(propylene glycol) copolymers dominate in the topical drug products. Out of the 34 topical drug products approved by the US FDA in 2014 under new drug application class, none contains a silicone material [82], however, silicones have been used in many monograph-supported/over-the-counter products. It is important not to ignore the time and cost associated with the approval process a new excipient, either silicone or nonsilicone-based, requires. But, the strong presence in the beauty care, and recent developments demonstrating enhanced drug delivery efficacy suggest a promising future for silicone technologies in the topical drug delivery arena.

Figure 2. *In vivo* delivery of anti-HIV drug maraviroc by silicone and hydroxyethylcellulose-based gels. Data shown are mean concentration $\pm$ SD (ng/ml) of maraviroc measured in the vaginal tissue of rhesus macaques following vaginal administration of a single 4 ml sample of 80/20 silicone elastomer gel or 2.2% w/w hydroxyethylcellulose gels containing 33 mg/ml maraviroc (100 mg total dose). Reproduced with permission from © Elsevier BV (2011) [44].

Silicones in transdermal drug delivery

The commercial success of transdermal drug delivery patches commenced in 1980 with the first commercial scopolamine patch to treat motion sickness [16]. Today drug delivery via skin is still an attractive delivery technology as witnessed by the number of product approvals in 2014. The key scientific attribute for this continuing success is the ability of the technology to provide sustained drug blood levels with minimal variation in blood levels of the active via a nonoral, noninjectable route of delivery [83]. The features and other advantages of **transdermal delivery** include the elimination of first pass metabolism over oral delivery and, painless and easy to use compared with hypodermic needles. Continuous drug delivery for up to a week via transdermal patches provide compelling and differentiating medical benefits that keep transdermal delivery an area of active research and product development.

The PSA is a critical component of the transdermal drug delivery system (TDDS) design irrespective of patch design, either matrix (or drug-in-adhesive) or reservoir. Recent trends almost exclusively favor matrix type patches elevating the significance of the adhesives' role not only as a skin interface to adhere the patch with the skin but also to play a key role in optimizing the

Key term

Transdermal delivery: Delivery of a drug through or across the skin beyond dermal layer.

delivery of the drug. In general, three adhesive chemistry sets are used in transdermal patches: polyacrylates, silicones and rubber, specifically polyisobutenes (PIB).

Silicone PSA

A family of noncompensial silicone excipients that has become widely accepted in TDDS is silicone PSAs. Silicone adhesives serve as a skin interface that holds the TDDS in place and/or act as the rate controlling matrices for the active. Medical PSA must provide secure adhesion for the prescribed duration and then have the ability to be removed cleanly from skin without causing undue trauma to the wearer [84]. The chain flexibility and open molecular structure with low molecular interactions that are inherent to silicone PSA provide the ability to wet out and conform to the contours of the skin surface as well as have suitable tack and adhesion for a variety of skin types. Adhesives designed for transdermal drug delivery must also show permeability to therapeutic ingredients while displaying minimal deleterious interactions with the drug and the other excipients and components of the transdermal device. Therefore, the PSA must maintain adhesive and cohesive properties in the presence of drugs that allow the patch to maintain intimate contact with the patient with a consistent geometry over the duration of the dosage regime [84]. Silicone PSAs offer excellent permeability to lipophilic drugs, and can be further modified by formulating with hydrophilic fillers, copolymers, plasticizers or by modification of the network with silicone-organic copolymers to also allow delivery of hydrophilic drugs.

Figure 3. *In vivo* delivery of ibuprofen to rats' blood. Data shown are the comparison of average ibuprofen blood concentration measured *in vivo* for S1 ($n = 5$) and benchmark ($n = 4$). S1 is silicone elastomer-based gel formulation and benchmark is a commercial gel product. Both S1 and benchmark contained ibuprofen at 5%.

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Silicone PSA are primarily based on PDMS materials, the product of the reaction between silanol end blocked dimethyl siloxane polymers and silicate resin. The polymers typically used are polydimethylsiloxanes with dimethylsilanol end groups, while the resins are 3D trimethylsiloxy and hydroxyl end-blocked silicate structures. The resin-to-polymer ratio and the degree of crosslinking are two of the most important performance-determining factors of the PSA. The resulting material from a simple blend of the resin and polymer will have some PSA properties, albeit with poor cohesive characteristics. This lack of cohesion can be overcome through a condensation (or bodying) reaction whereby the respective functional groups create a covalently bonded, crosslinked network. The adhesives created by this bodying reaction retain a relatively high degree of silanol functionality. These adhesives are suitable for many applications, including drug delivery for some actives. By reacting the residual silanol groups with a trimethylsilyl end capping agent, the silanol content can be significantly reduced to provide enhanced chemical compatibility. The resulting adhesives may be referred to as 'amine-compatible' and have found utility in transdermal patch applications because of their increased resistance to reactivity with amine functional drugs [84].

Silicone PSA was first used in the Duragesic® (Janssen Pharmaceuticals, Inc., NJ, USA) fentanyl patch in 1990 and its use in transdermal patch products continues today [85]. Table 1 provides the silicone-containing TDDS products approved in the USA in recent years and demonstrates the utility of silicone PSA in a variety of treatment modalities, both when used solo and in combination with other adhesive types [86].

Comparison of patch efficacy containing different PSAs

A recent survey of commercial fentanyl patches using three different adhesive chemistries; silicone, polyacrylate and PIB concluded that formulators could achieve bioequivalency of the drug dosage by formulating with any of the adhesive types, although with vastly different patch designs. However, commercial patches that made use of silicone or PIB adhesives exhibited more efficient utilization of the loaded drug (i.e., leaving less unused fentanyl in the patch). The efficient use of the drug also impacted the size of the patch where more efficient drug utilization typically required smaller patch size (equating to a smaller surface area of skin in contact with the patch). This phenomenon was attributed in large measure to the higher solubility of fentanyl in polyacrylate adhesives, which limited the likelihood of the drug passively eluting from the patch. This survey concluded that adhesives with lower drug

Table 1. US FDA-approved silicone-containing transdermal drug delivery system patch products in the USA (2000–2014).

Product name	Drug	Adhesive type
Clonidine Transdermal System	Clonidine	Silicone, polyacrylate
Daytrana® (Noven pharmaceuticals, FL, USA)	Methylphenidate	Polyacrylate, silicone
Fentanyl Transdermal System†	Fentanyl	Silicone
Fentanyl Transdermal System†	Fentanyl	Silicone
Fentanyl Transdermal System†	Fentanyl	Silicone
Fentanyl Transdermal System†	Fentanyl	Silicone
Fentanyl Transdermal System†	Fentanyl	Silicone
Minivelle® (Noven Pharmaceuticals)	Estradiol	Polyacrylate, silicone
Neupro® (UCB, Inc., GA, USA)	Rotigotine	Silicone
Qutenza® (Accorda Therapeutics, NY, USA)	Capsaicin	Silicone

†By different manufacturers/owners/distributors.

solubility may provide more efficient delivery attributes and therefore, should be preferentially selected when designing patches [85].

Achieving the therapeutically appropriate drug release profile that will support a commercial drug product is the ultimate factor that determines the relevance of a TDDS. Studies have investigated the permeation of many drugs from multiple adhesive matrices through different models and concluded that drug release from silicone matrices is generally higher than those from other tested adhesive matrices. This phenomenon is likely a result of lower interaction between the drug and the silicone PSA polymer compared with other adhesive polymers. The extent of the drug polymer interaction can be estimated by the relationship between the drug concentrations in the PSA and their diffusion coefficients. One such study investigated the interactions of four different drugs: dipropylphthalate, aminopyrine, ketoprofen and lidocaine in four adhesive matrices, two polyacrylate adhesives with differing functionalities, a PIB and an amine compatible silicone PSA. Interactions between the polyacrylate adhesives and some drugs were noted, but no drug–polymer interactions were noted with either the PIB or silicone adhesives which are composed of mostly nonpolar groups [87]. Another study identified the permeation of terbinafine across porcine hoof membrane and determined that drug permeation from the silicone matrix was the highest measured followed by PIB, polyacrylate adhesives and styrene block copolymer adhesives [88]. A separate analysis of *N*-methyl-D-aspartate, a receptor antagonist for neuropathic pain and neurological disorder, concluded silicone PSA would be the most suitable for the transdermal delivery of *N*-methyl-D-aspartate compared with other PSAs investigated (see Figure 4) [89].

Pharmaceutical formulators have utilized the diverse drug and polymer interactions inherent to the various adhesive technologies as well as the adhesive's dissimilar compatibility with drugs to create increasingly sophisticated TDDS designs. These have taken the form of layering silicone and other adhesives or other nonadhesive polymers that may act as drug reservoirs, or rate controlling layers within the seemingly monolithic TDDS to achieve the desired performance [85,90]. Other unique and advanced patch designs have been created by blending silicone adhesives with nonsilicone adhesives and other polymers with differing drug compatibilities to achieve patches with the desired therapeutic release profiles for a number of actives [91,92].

As the use of silicone PSA in the healthcare arena continues to expand in response to specific application needs, a number of publications describe compositions and/or constructions utilizing silicone PSA that are designed to provide delivery of specific drugs and improve safety through abuse deterrent TDDS dosage forms [93–95]. Patent literature discloses the use of silicone PSAs in transdermal patch development to deliver variety of drugs including NSAIDs [96–101], hormones [94,102–104], retinoids [105] and vitamins [105,106]. In most of these cases silicone PSAs have been noted for enhancing drug delivery in addition to other properties like less skin irritation and sensitization.

Hybrid silicone PSA

Two of the more commonly chosen adhesive types are the polyacrylate and silicone. Each adhesive chemistry type provides some advantages – silicone PSA may release active more readily, while the polyacrylate PSA have a greater affinity with many drugs and other common excipients, making formulating more straightforward. However, the converse of each advantage may

Key term

Residual drug: The amount of drug not utilized for the therapeutic purpose.

be a disadvantage, silicones may be more difficult to formulate due to the poor compatibility with a number of excipients and drugs, while drug release from the polyacrylate matrix is less efficient resulting in more **residual drug** in the used patch.

There have been several attempts to combine polyacrylate PSAs and silicone PSAs to gain the advantages of both technologies. Blending two types of PSAs or emulsifying in presence of surfactants generally provides phase separation and stability issues [107]. In this context, the concept of a silicone acrylate hybrid copolymer composition that retains the positive attributes of both PSA types has been put forward. At least two synthetic approaches have been suggested by different research groups by which silicone acrylate hybrid pressure sensitive adhesives for TDDS can be achieved [107,108]. Although, to date, neither approach has been commercially realized in a pharmaceutical product, it is an interesting silicone-based technology

that has gained much interest and is potentially on the horizon. The first approach recorded in the literature describes a multistep process by which a silicone PSA as described above is prepared, functionalized with a free-radical reactive agent, then acrylic monomer is added and then polymerized to create the hybrid copolymer [107]. This polymerization yields a PSA which chemically integrates the advantageous functionalities associated with both acrylic and silicone chemistries into a stable PSA that resists phase separation. The second technique to create the silicone acrylate copolymer hybrid uses prepolymerized acrylic polymer containing reactive silane groups and combining that with the precursors to the silicone PSA. During the final bodying step in the creation of the silicone PSA, the acrylates are grafted to the silicone [108]. Both techniques suggest that during polymerization, the silicone to acrylic ratio, the ratio and type of monomers chosen may be sufficiently controlled and optimized to achieve desired physical properties [107,108]. Similarly, the balance of silicone to acrylic components can be selectively used to control solubility of an active agent in the hybrid PSA to optimize the rate

Figure 4. Skin permeation of CNS5161 base (a *N*-methyl-D-aspartate) from pressure sensitive adhesives containing 10% CNS 5161. Data shown are the cumulative amounts of CNS5161 base, expressed as the mean with the bar shown standard deviation values of four experiments. Key: •, SIS(1); ○, SIS(2); ■, silicone; □, acrylate (OH); △, acrylate (COOH).

SIS: Styrene-isoprene-styrene block copolymers.

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at which the active agent is released from the system and also the amount of active agent that is ultimately released [107,108]. While the commercial utility of this technology is not totally understood today, derivations and applications outside TDDS are already appearing in literature as the nontacky adaptations of this technology have been suggested as film forming topical compositions [69].

While increased drug delivery efficiency may have an impact on the physical characteristics of a TDDS patch such as its size and shape, some regulatory and sustainability benefits may also be realized through more efficient formulations. A recent draft guidance by the FDA provided recommendations to developers and manufacturers of transdermal drug delivery systems, transmucosal drug delivery systems and topical patches to ensure that the residual drug content at the end of the product labeled use period is minimized [109]. More efficient delivery as evidenced by higher release rates of drugs from patches is not only aligned with this draft guidance, it may have implications when seeking regulatory approval for newly designed TDDS. In recent years, numerous reports have noted the presence of pharmaceutical and personal care actives in ground water [110,111], the impact of active pharmaceutical ingredients (API) on aquatic animal development [112], and the inability of current waste water and drinking water treatment facilities to remove API from treated water [113,114]. In the more efficient drug delivery formulations detailed above, less active was needed in the TDDS to achieve comparable therapeutic effect, and a higher proportion was utilized, making it likely that less drug will find its way into the environment from these devices. Efficient utilization of the drug has additional importance in some API like fentanyl due to unintentional use or abuse. The number of currently available fentanyl transdermal systems and the continuation of investigations [115–122] on the utilization of silicone PSAs for fentanyl patch development support the suitability of silicone PSAs when there is a need to deliver a drug efficiently.

Inspiring future

The unique inherent characteristics of the silicone materials, like hydrophobicity, wettability, low glass transition temperature have been continuously investigated to develop innovative materials and technologies for diverse applications. Irrespective of stringent requirements for all materials used in pharmaceutical drug delivery application, design and development of creative materials and technologies are always inspiring. Described below are a few of the very latest research reports which portray new developments using polysiloxane materials. Though they have not been directly

linked to topical/transdermal applications, they were indicated for potential drug delivery applications.

Tubular polysiloxane nanostructures were formed via a chemical vapor deposition technique at room temperature when ethyltrichlorosilane is used or via liquid phase method when methyltriethoxysilane is used as a precursor. The very low cost of synthetic method and nontoxic and inert nature of the polysiloxane materials make these tubes very attractive for many future applications including drug delivery [123].

An efficient and adaptable method for the microencapsulation of active ingredients by PDMS core-shell microcapsules has been reported by Teixeira *et al.* [124]. The microcapsule was obtained by phase separation between the core component and the PDMS shell components after repartitioning of the common solvent between the PDMS/core materials phase and the water phase. This microencapsulation provides environmental protection of the active ingredient and can also provide control and triggered release of the active. Drug delivery is known in which such microencapsulation can certainly be used.

A novel platform that allows for reliably attaching drug-loaded nanodepots to the surface of PDMS and releasing the drug in a sustained manner is demonstrated. The methodology is assisting to improve the hydrophilicity of PDMS surface, thereby improving the biocompatibility, without sacrificing the mechanical properties of PDMS. Though it is demonstrated with budesonide-loaded ethylcellulose nanoparticles, the platform could theoretically be applied to different PDMS medical devices and with other payload drugs [125].

Conclusion

PDMS-based silicone materials have been used in the medical industry over six decades. Dimethicone and simethicone are used as an active in many antacid/anti-gas drugs whereas many other silicones materials are used in pharmaceutical applications are excipients, particularly in topical and transdermal drug delivery systems. Unique characteristics including hydrophobicity, adhesion, low glass transition temperature, biocompatibility, aesthetics and a general resistance to many chemical degradation pathways allow silicones to offer function and performance to drug delivery products. Though silicones have a strong presence in the beauty care products, their use as a primary polymer in topically applied drug products is still infrequent. However, recent research reports on the role silicone may play in delivering drug efficiently in topical and transdermal drug delivery system applications and the vast numbers of patent filings suggest a promising future for silicone technologies in topical dosage forms with diverse therapeutic benefits. Moreover, new silicone

technologies like swollen crosslinked silicone elastomer blend networks, sugar siloxanes, amphiphilic resin linear polymers offer performance advantages and drug delivery efficacy improvements in topical or transdermal drug delivery systems. Silicones, as PSA, already have an impressive presence in transdermal drug delivery system products. Silicone PSAs are often the choice when efficient drug delivery from the patch is required. However, the solubility of the drug in the silicone matrix is often insufficient and remains a challenge for wider acceptance of silicone PSA. Recently introduced silicone hybrid PSA materials may provide a solution to this situation and also enhance compatibility with other excipients in the formulation.

Future perspective

The history of silicone ingredients in the personal care products has established their suitability in topically applied products. Though the regulatory status does not favor their selection by the formulators, research suggests that silicone materials may have a role to play in delivering drugs more efficiently. This scenario coupled with the demand from healthcare consumer for efficient and aesthetically pleasing topically applied products may bode well for the future of novel silicone excipients as platforms in topical drug products. Properties like film formation and enhanced compatibility with organic materials that are inherent in some new silicone technologies in addition to the intrinsic aesthetic characteristics, could further support the use of more silicone materials in topical drug products in the future.

Silicone-based pressure-sensitive adhesives have already made a valuable contribution in transdermal drug delivery system products. It is easily observed from the literature that silicone PSAs are selected when efficient delivery from the patch is required; however the solubility of the drug often in the silicone matrix is insufficient. Recently introduced hybrid silicone PSA materials may provide a solution to this situation. Regulatory authorities' insistence for efficient use of drugs in the patch products, new hybrid silicone PSA and silicone PSA's efficient drug delivery in general, would make the silicone PSAs as preferred adhesives in the future TDDS product development.

Though topical and transdermal product development mostly focuses with low molecular weight drugs currently, when the technology is developed and/or established for delivering high molecular weight active like biologics, proteins, vaccines transdermally in the future, silicone-based excipients may play an important role in delivering them either topically or transdermally in the future.

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Executive summary

Silicones in medical applications

- Polydimethylsiloxane-based silicone materials have been used in medical applications over 60 years.
- Dimethicone and simethicone are only two silicone-based materials used as actives for therapeutic purpose; they have also been used as excipients in many drug products; all other silicone materials used in the pharmaceutical drug delivery products are excipients.

Benefit of silicones in topical formulations

- Silicone-based materials are used exhaustively in cosmetic or beauty care topical products; however, their use as a primary polymer in topical drug delivery products is infrequent.
- Recent investigations have demonstrated that silicone materials could assist to deliver the drug efficiently from topical dosage forms compared with nonsilicone-based polymeric materials.
- Silicone excipients in the form of low to high molecular weight liquid, pastes and solids have been investigated in topical formulations of different dosage forms using different types of active pharmaceutical ingredients.
- Silicone topical excipients could provide hydrophobicity, nonocclusivity or semi-occlusivity and film formation.

Silicone pressure sensitive adhesives: current presence, benefits & new hybrid technology

- Silicone-based pressure sensitive adhesive (PSA) materials have made their significance via many approved transdermal drug delivery patch products.
- Silicone PSAs come with variety of tack properties and in different solvents.
- Select PSAs are recommended for amine-containing drugs.
- Silicone PSAs have been used preferentially when there is a need to deliver the drug efficiently.
- Silicone PSAs provide good biocompatibility to skin and stability to the transdermal drug formulations.
- Hybrid silicone PSAs offer unique properties for drug solubility, drug delivery and stability compared with corresponding blend of two individual PSAs.

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