Recent Developments on Silicones in Topical and Transdermal Drug Delivery

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ABSTRACT

Silicones have been used in medicines, cosmetics and medical devices for over 60 years. Polydimethylsiloxanes (PDMS) are the most commonly used polymers either as an active in many oral anti-acid/anti-gas drugs or in different physical forms as excipients in topical and transdermal drug delivery systems. Characteristics like hydrophobicity, adhesion and unique aesthetics allow silicones to offer function and performance to drug delivery products. The investigation of silicones for well-differentiated and novel applications continues to progress irrespective of the regulatory hurdles prior to being used in an approved product. Such investigations have revealed that silicones have merit for functional characteristics and also to enhance drug delivery efficacy of topical and transdermal products. Recent silicone technologies like swollen crosslinked silicone elastomer blend networks, and silicone-based hybrid pressure sensitive adhesives promise potential performance advantages and improved drug delivery efficacy in topical or transdermal drug delivery systems. This article presents a review of recent silicone material developments for topical and transdermal drug delivery applications.

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INTRODUCTION

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 [1]. The multitude of physical forms and the physiochemical properties that silicones can display have led to their adoption in a diverse array of healthcare applications. The silicone chemistry is known and has been well documented in a variety of previous texts [2-4].

This article describes advances in the application of silicone polymers in the pharmaceutical field, with an emphasis on topical and transdermal drug delivery.

Dimethicone and simethicone

Multiple monographs describe a common linear siloxane polymer under different names. The NF monograph for dimethicone, the EP monograph for dimeticonum or dimeticone all describe essentially the same polymer. The USP terminology will be adopted for this discussion, and this group of polymers will be referred to as dimethicone within this work. Dimethicone is chemically defined as being a fully methylated linear siloxane polymer containing repeating units of the formula $[-(CH_3)_2SiO-]_n$ with trimethylsiloxy end block units of the formula $[(CH_3)_3-SiO-]$. To comply with the monographs, the number of repeating units must have an average value such that the corresponding specific nominal viscosity of the polymer is between 20 and 12,500 cSt. All of these monographs describe what is likely the most common silicone polymer used in pharmaceutical applications. The polymers with a viscosity greater than 20 cSt are expected to contain less volatile content than those whose viscosity is 20 cSt. Increases in refractive index and specific gravity are also expected as chain lengths (and viscosity) increase [5].

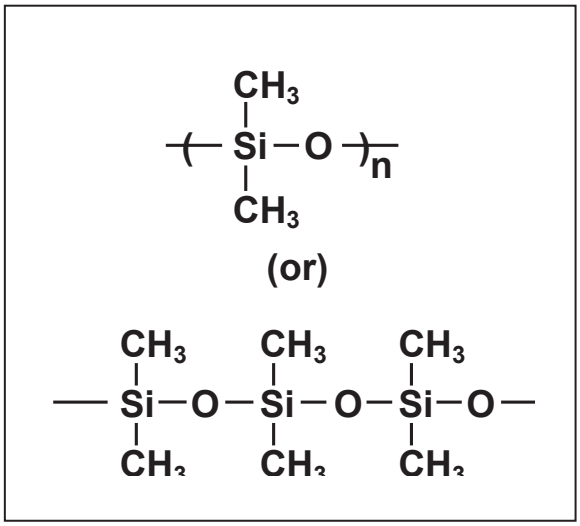

Figure 1. The chemical structures of polydimethylsiloxane (PDMS)

Like most silicones, dimethicone is hydrophobic and repels water. Dimethicone polymers find utility in many topical formulations (e.g., creams, lotions, etc.) where water resistance is key to performance. Dimethicone is substantive when applied to the skin and forms a barrier to regular soap and water that may last for several hours when exposed to primarily aqueous media, but it is a less effective barrier against lipid-soluble agents and synthetic detergents [6]. Dimethicone is specified by the United States Food and Drug Administration (USFDA) monograph describing over-the-counter (OTC) skin protectant drugs, so products containing from 1 to 30% dimethicone of the total composition can claim skin protectancy under this monograph [7]. This is a common usage of dimethicone, and it can be incorporated into many final product forms, including

sticks, creams, lotions and ointments, either as the only active or in combination with others [6]. Dimethicone is especially prevalent in incontinence barrier products for both adults and children and is also a common ingredient in products intended for the treatment of diaper rash and prickly heat that claim to be non-allergenic and non-sensitizing [6, 8]. Dimethicone emulsions as either creams or lotions are also well known in the pharmaceutical industry, and the process and general formulary composition are well known and described [9]. These silicone emulsions are utilized in the treatment of several indications, including acne, fungal diseases and psoriasis as well as other skin conditions [10]. Dimethicone has long been considered non-comedogenic, which may explain the use in acne remedies [11].

A variety of silicones, including dimethicone and dimethicone emulsions in particular, are known to be used in siliconization, the lubrication of syringes, plungers, needles and the like by a thin layer of silicone [12]. It has been noted that siliconized needles moved through the skin with less force and caused less pain to patients than uncoated needles. Silicones were first used to coat a glass vial interior in 1950 [13]. Today, siliconized needles are widely accepted and most hypodermic needles and syringes are coated and/or lubricated with silicone [12].

A monograph also exists for a silicone active pharmaceutical ingredient (API). The USP describes simethicone as a mixture of fully methylated linear siloxane polymers containing repeating units of the formula $[-(CH_3)_2SiO-]_n$ stabilized with trimethylsiloxy end block units of the formula $[(CH_3)_3-SiO-]$ and between 4 and 7% silicon dioxide. In addition to a monograph for simethicone raw material, the USP also contains monographs for finished products that utilize simethicone, including capsules, emulsions and oral suspensions. Simethicone is widely available as the active ingredient, under many brand names, generally as OTC orally ingested antacids [8]. Simethicone decreases the surface tension of gas bubbles, causing them to combine in the stomach which can be passed away more easily. Simethicone does not reduce the formation of gas.

Although the monographs describe simethicone as the active ingredient in a variety of liquid or solid dosage forms, simethicone has also been described in recent patent literature for other pharmaceutical applications where simethicone is used as a process aid or an intentionally added excipient. The commercial viability of some of these ideas is uncertain, but it provides a snapshot of potential uses considered worthwhile enough to seek intellectual property protection. Given the widespread use of simethicone as a defoaming agent and the inherent lubricity of silicones, it is not surprising to note that researchers have suggested simethicone being used as a defoaming agent in protein fermentation processes to increase yields [14], as a lubricant to prevent and reduce mold fouling in pharmaceutical tablet or lozenge manufacturing [15], and as an excipient to ease difficulties associated with swallowing [16]. Although simethicone has traditionally been used in oral delivery, its selection as an excipient may not be limited to those delivery forms; it has also been suggested as an excipient in topical products, including nanoemulsion formulations for topical anti-fungal treatments [17] and topically applied skin whiteners [18]. A recent search of database for inactive ingredients in topical formulations found several instances of simethicone in anti-acne products [19].

Silicones in topical drug delivery

The use of silicone materials in many topical products has beenreported [11]. 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 [20-22]. 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 impressive contributions to pharmaceutical drug delivery applications as well. A recent estimate is that over 50% of current skin care products contain at least one silicone material [21, 23]. 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 [23-25].

Silicone-containing emulsion compositions were reported to deliver several actives, including niacinamide [26], thiazolinium compounds [27] and chlorhexidine [28] 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 [29]. 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 PDMS (silicone gum) [30], or pressure sensitive adhesives (PSAs) using polymeric surfactant like ethylene oxide-propylene oxide block copolymer [31], have also demonstrated utility in topical drug delivery applications.

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 non-irritation [32], moisture maintenance and solubilization of the active [33]. Actives, including 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 [34-35].

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 [36]. Today, drug delivery via skin is still an attractive delivery technology as witnessed by

the number of product approvals. The key scientific attribute for this continuing success is the ability of the technology to provide sustained drug concentrations in the blood with minimal variation via a non-oral, non-injectable route of delivery [37]. The features and other advantages of transdermal delivery include the elimination of first-pass metabolism over oral delivery and painlessness and ease of use compared to 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 pressure sensitive adhesive (PSA) is a critical component of the transdermal drug delivery system (TDDS) irrespective of patch design. Recent trends favor matrix-type patches, elevating the significance of the adhesive's role not only as a skin interface to adhere the patch with the skin but also to play a key role in optimizing the delivery of the drug. Silicone adhesives in a TDDS may serve as a skin interface that holds the TDDS in place and/or act as 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 [38]. The PDMS chain flexibility and the open polymer 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 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 regimen [38]. Silicone PSAs offer excellent permeability to lipophilic drugs, and can be further modified by formulating with hydrophilic fillers, copolymers and plasticizers, or by modification of the network with silicone-organic copolymers to also allow delivery of hydrophilic drugs.

Silicone PSAs are primarily based on PDMS materials, the product of the reaction between silanol end-blocked dimethyl-siloxane polymers and silicate resin. The polymers typically usedare polydimethlysiloxanes with dimethlysilanol end groups, while the resins are three-dimensional 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 over-come 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 endcapping 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 [38].

Silicone PSA was first used in the *Duragesic*® fentanyl patch in 1990, and its use in transdermal patch products continues today in a variety of treatment modalities and patch designs [39-40].

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 and polymer interaction can be estimated by the relationship between the drug concentrations in the PSA and their diffusion coefficients.

Pharmaceutical formulators have utilized the diverse drug and polymer interactions inherent to the various adhesive technologies as well as the adhesive's varying miscibility with drugs to create increasingly sophisticated TDDS designs. These have taken the form of layering silicone and other adhesives or non-adhesive polymers that may act as drug reservoirs, or rate-controlling layers within the seemingly monolithic TDDS to achieve the desired performance [39, 41]. Other unique and advanced patch designs have been created by blending silicone adhesives with non-silicone adhesives and other polymers with differing drug compatibilities to achieve patches with the desired therapeutic release profiles for a number of actives [42-43].

As the use of silicone PSA in the healthcare arena continues to expand in response to specific application needs, a number of publications have described 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 [44-46]. Patent literature discloses the use of silicone PSAs in patch developments to deliver a variety of drugs, including non-steroidal anti-inflammatory drugs (NSAID) [47-52], hormones [45, 53-55], retinoids and vitamins [56-57]. In many of these cases, silicone PSAs have been noted for enhancing drug delivery in addition to other properties like less skin irritation and sensitization.

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

may 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 [58]. 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. Although multiple synthetic approaches have been suggested by which silicone acrylate hybrid pressure sensitive adhesives for a TDDS can be achieved, the first approach recorded in the literature describes a multi-step 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 [58]. 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. During polymerization, the ratio and type of acrylic monomers, the silicone to acrylic ratio, chosen may be sufficiently controlled and optimized to achieve desired physical properties [58]. 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 at which the active agent is released from the system and the amount of active agent that is ultimately released [58]. Although, to date, this new adhesive technology has not 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.

Inspiring future

Advancements 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 utility 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. Detailed below are some technologies and materials that have been recently reported and relate to topical pharmaceutical drug delivery applications.

Silicone elastomer blends (SEB) are slightly crosslinked, three-dimensional polymer networks swollen in an appropriate 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 topically applied formulations to efficiently deliver drugs. Forbes *et al.* reported efficient *in vivo* delivery of an antiretroviral

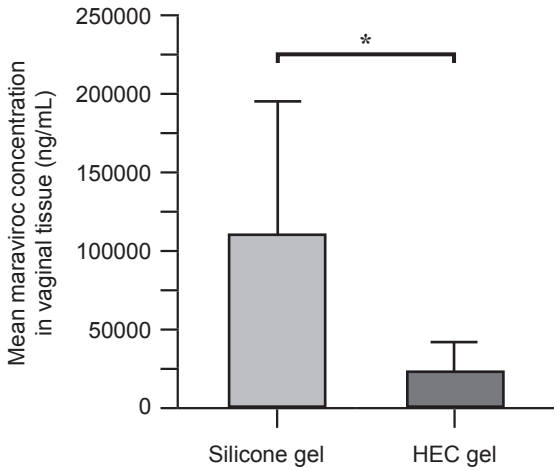

Figure 2. In vivo delivery of anti-HIV drug maraviroc by silicone and hydroxyethylcellulose (HEC) based gels. Data shown is mean concentration ±SD (ng/mL) of maraviroc measures in the vaginal tissues of rhesus macaques following vaginal administration of a single 4 mL sample of 80/20 silicone elastomer gel or 2.2% w/w HEC gels containing 33 mg/mL maraviroc (100 mg total dose). Reproduced with permission from ©2011 Elsevier B.V.

silicone materials have been utilized to make non-aqueous, human immunodeficiency virus (HIV) drug, maraviroc, to shearing the gels into discrete particles [59-60]. These semi-solid rhesus macaques from a non-aqueous silicone elastomer gel formulation over non-silicone-based formulation(s) pertinent to a microbicide delivery system (see Figure 2) [61]. 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 hours and less cytotoxicity compared to standard hydroxyethylcellulose gels [62]. The non-aqueous 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 a silicone elastomer-based gel formulation compared to a commercial product [63]. 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 [64], retinoic acid derivatives [65], amino acids [66], antiperspirants [67], clobetasol propionate [68] and several other actives [69-70]. Crosslinked silicone matrix-type

polymers were reported for the encapsulation and subsequent delivery of actives for improved stability and performance [71], and in some instances to deliver protein [72-73]. Using different types of silicone elastomer gels, dual drug delivery, delivery of hydrophilic and hydrophobic drugs from gel formulations have also been reported [74].

Soft skin adhesive (SSA) technology 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 [75]. The loosely crosslinked structure has proven its suitability for topical drug delivery as well. The patches made from SSA showed noteworthy 24 hours of cumulative release of 45 to 58% estradiol compared to 1 to 12% by other polymers over the same period of 24 hours [76].

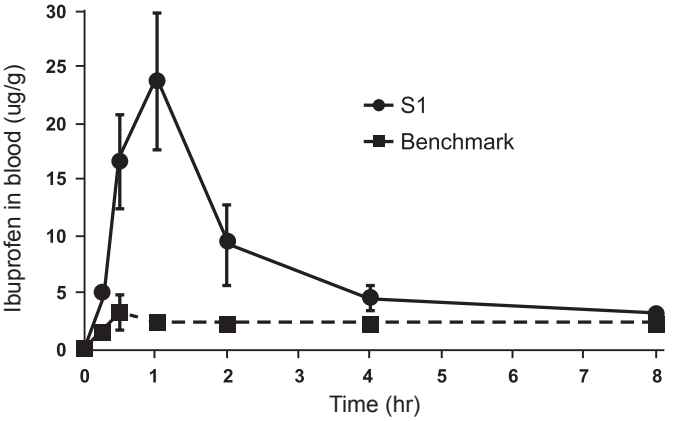

Figure 3. In vivo delivery of ibuprofen to rats' blood. Data shown is the comparison of average ibuprofen blood concentration measured in vivo for S1 (n=5) and benchmark (n=4). S1 is silicone elastomer-based gel formulation and benchmark is a commercial gel product. Both S1 and benchmark contained ibuprofen at 5%. Reproduced with permission from ©2014 Wiley Periodicals, Inc., and the American Pharmacists Association.

Conclusion

Polydimethylsiloxanes (PDMS) based silicone materials have been used in the medical industry for over six decades. Dimethicone and simethicone are the active pharmaceutical ingredient in many anti-acid/anti-gas drugs, whereas many other silicone materials 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. Recent research reports on the role silicone may play in delivering drugs efficiently in topical and transdermal drug delivery system applications, and the vast numbers of patent filings suggest a promising future for silicone technologies in a variety of pharmaceutical dosage forms with diverse therapeutic benefits. Moreover, new silicone technologies like swollen crosslinked silicone elastomer blend networks, copolymer pressure sensitive adhesives, and crosslinked gel-like soft skin adhesives offer performance advantages and drug delivery efficacy improvements in topical or transdermal drug delivery systems.

Executive summary

- Polydimethylsiloxane (PDMS) based silicone materials have been used in medical applications for over 60 years.
- Dimethicone and simethicone are 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.
- 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 less frequent.
- Recent investigations have demonstrated that silicone materials could assist to deliver the drug efficiently from topical dosage forms compared to non-silicone-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 APIs.
- Silicone topical excipients could provide hydrophobicity, non-occlusivity or semi-occlusivity, and film formation.
- Silicone-based pressure sensitive adhesive (PSA) materials have made their significance via many approved transdermal drug delivery patch products.
- Silicone PSAs come with a 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, delivery and stability compared to corresponding blend of two individual PSAs.

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