

17. Silicones in Medical Applications

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Silicone materials celebrate 60 years of use in medical applications. Quickly after their commercial availability in 1946, methylchlorosilanes were described to treat glassware to prevent blood from clotting [1]. At the same time, Dr. F. Lahey implanted a silicone elastomer tube for duct repair in biliary surgery [2]. Since these pioneers, the interest for silicones in medical applications has remained because of their recognized biocompatibility. Silicones are used today in many life-saving medical devices like pacemakers or hydrocephalic shunts [3]. Silicones are also used in many pharmaceutical applications from process aids like tubing used to manufacture pharmaceuticals, to excipients in topical formulations or adhesives to affix transdermal drug delivery systems [4]. They also have found use as active pharmaceutical ingredients in products such as antacid and antifatulent formulations [5-6].

Polydimethylsiloxanes and Biocompatibility

In medical devices and pharmaceutical applications, silicones are used because of their biocompatibility in a wide variety of physical forms. These forms range from volatile and low oligomers to high molecular weight polymers with viscosities from 0.65 cSt to 20×10^6 cSt to viscoelastic compounds and cross-linked elastomers.

Biocompatibility is defined as “the ability of a material to perform with an appropriate host response in a specific situation” [7-8]. The impact of the biomaterial on its host environment is assessed according to approved standards (e.g., ISO 10993, USP and European monographs) aligned with the performance requirements for the intended applications. Overall, medical grade silicones, and in particular PDMS fluids or PDMS-based elastomers, satisfy the criteria of the above standards, including nonirritating and nonsensitizing behaviors, which explain their wide use in personal care and skin topical applications. A long history of use in medical devices, including long term implants, has made silicones widely recognized as biocompatible. These standards are yet addressing the impact from the host on the foreign material to a lesser extent, as data on biodurability are difficult to acquire. But again, silicones perform well as demonstrated by studies on PDMS-based elastomers explanted and showing good biodurability (Table 1, page 704 in [3]).

Silicones with side-chain groups other than methyl (Me) are less used; PDMS polymers are the “preferred material,” even if some unlisted non Compendia/non Pharmacopoeia materials are now also well established (e.g., silicone pressure sensitive adhesives for transdermal systems). Potential improvements with new silicones are hindered by rigid regulatory requirements, and innovation is sometimes limited to the use of current materials in new applications.

Linking physicochemical properties to biocompatibility is not yet fully understood for many materials. Various factors are involved to explain the successful use of PDMS-based materials in medical devices or pharmaceutical applications:

- Because of their backbone flexibility, PDMS materials can preferably expose their low interacting Me group substituents at many interfaces, leading to low surface tension, low surface energy and low intermolecular interactions, resulting in a low overall level of interactions at their surfaces. Therefore PDMS materials are among

- the most favored polymers when considering biocompatibility [9].
- Their composition is well established. PDMS polymers do not require stabilizers because of their intrinsic stability. PDMS elastomers do not require plasticizers because of their low T_g . Hemocompatibility studies have suggested that silicone tubing may be superior to PVC tubing [10]. Impurities are well characterized siloxane oligomers and the toxicology profile of these oligomers has been investigated recently in detail. Other impurities are catalyst traces, such as acids or bases used in polymerization, but these are easy to eliminate and usually not an issue. Similarly, traces of platinum catalyst used at very low levels in cross-linking reactions may be present (platinum content 5 ppm to 20 ppm), and again this is usually not an issue. Only some tin catalysts used in room temperature curing materials or byproducts of peroxides used as initiators in some high consistency rubbers (HCR) have raised concerns [3].

Medical Devices and Pharmaceuticals

Apart from their prevailing biocompatibility, other properties contribute to the use of silicones in medical and pharmaceutical applications:

- Because of their low liquid surface tension around 20.4 mN/m and slightly higher critical surface tension of wetting of 24 mN/m, PDMS polymers spread easily to form films over substrates like skin but also spread over their own absorbed film.
- Because of their viscoelastic behavior, resin-reinforced silicones or partially cross-linked elastomers (e.g. gels) have pressure sensitive properties. Their soft, rubbery behavior makes such silicones very appropriate materials for contacting biological tissues by minimizing the risk of trauma at the interface (e.g., low skin stripping force, gentle removability, no adhesion to wound bed). This allows their use in transdermal drug delivery and wound management applications to secure patches or dressings to the skin with minimum impact on the contacting area [11].
- Because of their high permeability, silicones allow the diffusion of many substances such as gases (i.e., oxygen, carbon dioxide, water vapor) but also the diffusion of various actives (i.e., plant extract, drug, or even protein). This explains their use in personal care, skin topical applications or wound dressings (nonocclusive properties, no maceration) [12]. It also explains their use as adhesives or elastomers in controlled drug delivery systems [13-14-15-16].

Another practical aspect should not be ignored. Because of their stability, silicones are easy to sterilize by steam or ETO. Gamma or beta radiation sterilization require more precautions as they can induce radical reactions [17].

Overall, it is often an association of properties that supports the use of silicones in medical applications (see Table 1) [18-19].

Table 1. Correlations between Silicone Materials, Performance and Applications

<i>Silicone Materials</i>	<i>Key Physical Characteristics and Performance</i>	<i>Medical and Pharmaceutical Applications</i>
Fluids <ul style="list-style-type: none"> • Polydimethylsiloxane • Organofunctional siloxane <ul style="list-style-type: none"> - Silicone polyether - Silicone alkyl wax 	<ul style="list-style-type: none"> • Spreadability, film-forming • Diluent, dispersing property • Substantivity • Controlled occlusivity • Hydrophobicity • Lubricant property • Emulsifying property 	<ul style="list-style-type: none"> • Siliconization of needles and syringes • Medical device lubrication • Excipients for topical formulations • Skin protecting composition • Drug carrier
Compounds <ul style="list-style-type: none"> • Silica + polydimethylsiloxanes 	<ul style="list-style-type: none"> • Antifoam • Diluent, dispersing property 	<ul style="list-style-type: none"> • Antiflatulent (APIs)
Gels (unreinforced elastomers) <ul style="list-style-type: none"> • Cross-linked polydimethylsiloxanes 	<ul style="list-style-type: none"> • Softness • Resilience • Tackiness • Transparency • Adjustable cure conditions: from ambient to elevated temperature • Foamable 	<ul style="list-style-type: none"> • Cushioning material • Gentle adhesive for skin (soft skin adhesive) • Wound interface (nonadherent wound dressing, foam dressing) • Soft matrix for drug release
Elastomers <ul style="list-style-type: none"> • Cross-linked polydimethylsiloxanes • Reinforced with silica • Various cure system: radical, hydrosilylation, condensation 	<ul style="list-style-type: none"> • Rubbery property • Mechanical resistance • Adjustable modulus • Adjustable cure conditions: from ambient to elevated temperature • Adjustable cross-linking conditions • Foamable • In-situ film-forming 	<ul style="list-style-type: none"> • Soft and resilient material for medical device • Recognized biocompatibility for human implantation (e.g., pacemaker) • Medical adhesive (sealant) • Film-former
Pressure sensitive adhesives (PSAs) <ul style="list-style-type: none"> • Silicate resin in polydimethylsiloxanes 	<ul style="list-style-type: none"> • Tacky material • Adhesion to skin and various substrates (e.g., plastic films) • Substantive film-forming 	<ul style="list-style-type: none"> • Temporary fixation of devices on the skin (e.g., wig, catheter) • Film-former • Transdermal drug delivery system

Medical Devices. Contradictory to pharmaceuticals, medical devices are articles or associations of articles used in health care to support therapeutic treatments and assist patient life without pharmacological effects and interferences with biological processes. Silicones are used as components or fabricating materials in many such devices.

Silicone fluids are used to lubricate or “siliconize” many medical surfaces like syringe pistons and barrels. The result is reduced “jerk” during injections or on needles, thus reducing pain [1-8, 10-20].

Silicone polymers are easily converted into elastomers by creating covalent bonds between adjacent macromolecules to form three-dimensional networks [21]. Various chemical reactions are available to cross-link or cure silicone polymers:

- Condensation cure between hydroxy, alkoxy or acetoxy groups in presence of tin or titanium catalysts, with liberation of water, alcohol or acetic acid and formation of Si-O-Si bonds
- Radical initiated cure and reactions between alkyl and/or alkylene groups using peroxide to form Si-alkyl-Si bonds, but requiring post-cure to eliminate peroxide byproducts
- Addition cure or hydrosilylation of vinyl functional polymers by hydrogen functional siloxanes in the presence of platinum catalyst to form Si-CH₂-CH₂-Si bonds; in many applications, this reaction is preferred (addition reaction without byproducts; low level of Pt catalyst: 5 ppm to 20 ppm as Pt)

Physical properties are adjusted by controlling the cross-linking density and using reinforcing fillers, usually fume silica. Barium sulfate is added when radiopacity is required.

Because cross-linking points are far apart, dimethylsiloxane segments are most likely to be exposed on the surface of these elastomers, so elastomers display the good biocompatibility associated with PDMS fluids.

Various methods are used like casting, molding and injection to produce parts, or extrusion to produce tubing. Applications range from short term, noninvasive devices to critical, long term devices and are as diverse as long term implants like mammary implants (not without controversy), pacemaker leads, peristaltic tubing in heart-bypass machines or hydrocephalus shunts for regulating cerebrospinal brain fluid (see Figure 1) [3-22-23-24].

Silicone coatings (solvent-based elastomer dispersion) are also used over other materials like natural latex to reduce adverse effects (see Figure 2).



Figure 1. Long term implant: silicone elastomer valve and tubing of a hydrocephalic shunt (Picture courtesy of Medos, a Johnson & Johnson company).

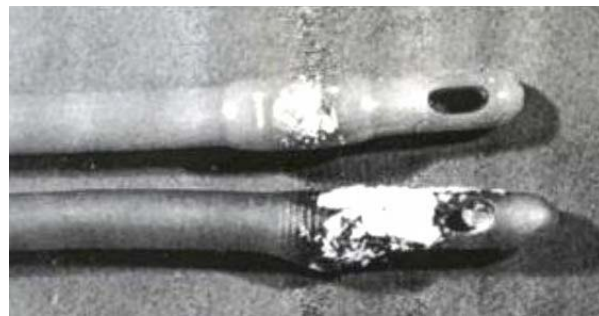


Figure 2. Short term implant: comparison of the incrustation on a silicone-coated latex catheter (top) vs. a latex catheter (bottom) (Picture courtesy Dow Corning).

Silicone gels, adhesives and foams are part of various wound dressings used to reduce nursing costs, but also to improve comfort and therapy [25]. Silicone gels in particular have been successful in this case. These soft, relatively cohesive and tacky gels are platinum-cured elastomers without reinforcing fillers and are used:

- As filling materials in cushions to prevent pressure sores
- In wound dressings because of their permeability to oxygen and water vapor (no maceration dressing), with gentle adhesion to skin around a wound, but with nonadherence to damaged tissues and the healing wound bed
- In scar treatment where a dressing such as silicone gel sheeting has demonstrated its efficacy for the treatment of keloid and hypertrophic scars, as confirmed by various studies including a meta-study [26-27].
- More recently, the release of actives from adhesives has been investigated with enzymes for the debridement of necrotic tissues [12].

Pharmaceutical Process Aids. Silicones are commonly used as process aids in the production of pharmaceuticals like:

- Silanes as temporary protective agents in the synthesis of complex molecules such as antibiotics (e.g., penicillin or cephalosporin). Specific groups are protected by silylation (e.g., carbinols reacted with trimethylchlorosilanes to form a Si-O-C bond later easily hydrolyzed to recover the active molecule) [28-29]
- Antifoams in fermentation process
- Silicone tubing used to prepare drugs or vaccines in various fluid transfer operations,

peristaltic pumping and filling operations. This tubing helps reduce investment costs in fixed stainless steel lines and, particularly for single-use applications, to eliminate costs associated with validation of cleaning-in-place (CIP) or sterilization-in-place (SIP) and disposal of contaminated waste waters [30-31-32]. Innovative biotech processes take advantage of silicone elastomer properties such as their gas permeability in fermentation cell systems, in which the oxygenation is directly achieved via gas permeation through the silicone tubing wall [19].

Pharmaceutical Ingredients. Silicones are present in many pharmaceutical finished drug products, and more than 350 products containing silicones are listed in various compendia [33].

Cyclics (Cyclomethicone NF) are used in topical products because of their good spreading and volatility, with low heats of evaporation per gram of formulation (resulting in no cooling effect on the skin) [33].

In the US, silicone fluids (Dimethicone NF) around 1,000 cSt are recognized as skin protectants for use in over-the-counter products [34]. This benefit is exploited in creams and ointments, and is most likely due to the high spreadability and high hydrophobicity of PDMS.

Increasing the molecular weight, using PDMS gums (fluids with viscosity around or higher than 600,000 cSt) leads to interesting film-forming materials that are transparent, long-lasting on the skin and capable of improving the substantivity of personal care ingredients as sunscreens or active pharmaceutical ingredients (APIs) (e.g., ketoprofen) [35].

Polydimethylsiloxanes alone (dimethicone) or compounded with silica (simethicone) are used in gastroenterology for their antifoam properties. They reduce foaming in the stomach without modifying the gastric pH, and are thus used in many antifatulent/antacid products, in particular in countries using hot spices. They are considered an API, but their mode of action is physical; they are not metabolized but excreted as such [36].

Silicone pressure sensitive adhesives (PSAs), which are PDMS/silicone resin networks, are used in numerous transdermal drug delivery systems (TDDS) to fix the drug device onto the skin (see Figure 3) [37]. These are viscoelastic compounds in which the PDMS fluid contributes to the wetting and spreadability of the adhesive and the resin, acting as the reinforcing agent, to the elastic rheological component. Because of the PDMS permeability, these PSAs allow the slow and controlled diffusion of various actives for various treatments: nitroglycerin (angina pectoris), estradiol (hormone replacement), fentanyl (pain management) and others. Both reservoir and matrix systems are known, the latter often considered because of its greater construction simplicity [37].

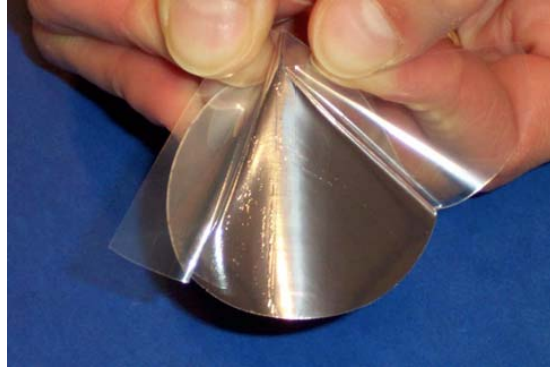


Figure 3. *Transdermal drug delivery system or patch with a silicone pressure sensitive adhesive (Picture courtesy Dow Corning).*

Silicone elastomers are used in drug-loaded pharmaceutical devices for the release of various APIs such as levonorgestrel in a subcutaneous contraceptive implant or 17 beta-estradiol in a vaginal ring for the treatment of urinary problems associated with menopause. In these reservoir devices, the release of the API is controlled by the permeability of the PDMS cross-linked network [36].

In all the above applications, silicones have been considered because of their contribution to biocompatibility (medical devices), ease of use (pharmaceutical process aids) or improvement of comfort and/or treatment, allowing lower and local dosage forms with fewer side effects or making wound dressings easier to apply for potentially better compliance [37].

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