Silicones in Pharmaceutical Applications.

Part 1: Silicone Chemistry

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Abstract
Silicones are currently used in many different healthcare applications, including registered pharmaceutical products (as both actives for anti-acid formulations and as excipients for topical creams and drug loaded devices) and pharmaceutical process aids (e.g. defoamers for foam control and tubing for pharmaceutical transport and filling operations). Silicones are specially suitable for use in pharmaceutical applications because of their unique physicochemical properties (e.g. low surface tension, high permeability to gases and drugs, non-greasy feel, etc.). This article is targeted at providing a general review of the chemistry involved in producing silicone fluids, elastomers, gels and adhesives targeted for use in healthcare applications as well as a review of some of their physiological, toxicological and environmental properties.

1. Introduction
By analogy with ketones, the name “silicone” was given in 1901 by Kipping to describe new compounds of the brut formula R₂SiO. These were rapidly identified as being polymeric and actually corresponding to polydialkylsiloxanes, with the formulation:

\[
\left[ \begin{array}{c}
\text{R} \\
\text{Si} \\
\text{O} \\
\text{R}
\end{array} \right]_n
\]

The name silicone was adopted by the industry and usually refers to linear polymers where R = Me or polydimethylsiloxane (PDMS):

\[
\ldots \text{Me-Si-O-} \text{Me-Si-O-} \text{Me-Si-O-} \ldots \text{or} \left[ \begin{array}{c}
\text{Me} \\
\text{Si} \\
\text{O} \\
\text{Me}
\end{array} \right]_n
\]

Numerous other structures can easily be obtained, either by substitution of methyl groups by other groups like -CH = CH₂, -H, -CH₂CH₂CF₃ or by replacing some of the Me₂SiO₂/₂ chain units with Me-SiO₃/₂ or SiO₄/₂ units where the silicon is substituted with 3 or 4 oxygen atoms to give non-linear branched structures. The simultaneous presence of “organic” groups attached to an “inorganic” backbone gives silicones a combination of unique properties and allows their use in fields as different as aerospace (low and high temperature performance), electronics (electrical insulation), health care (excellent biocompatibility) or in the building industries (resistance to weathering). The preferred polymers for pharmaceutical applications are the ones essentially substituted by methyl groups.

2. Synthesis
Pharmaceutical applications utilize a broad range of silicone technologies targeted for application as: topical excipients, skin adhesives, elastomeric matrices, in situ film-formers, coatings, fluids and emulsions. Silicone solutions often involve the use of: fluids and gums (linear and/or cyclic siloxane monomers and polymers), cross-linked silicone elastomers and silicone pressure sensitive adhesives.

2.1 Fluids and gums
Both low and high molecular weight reactive/non-reactive silicone fluids and gums are prepared via the following synthetic step(s).

2.1.1 Dimethyldichlorosilane synthesis
Chlorosilanes are commercially produced today following the direct process of Rochow which involves reacting silicon metal (obtained from the reduction of sand at high temperatures in the presence of carbon in an electronic arc furnace) with methyl chloride. The reaction takes place in a fluidized bed reactor to produce a mixture of silanes for which dimethyldichlorosilane, Me₂SiCl₂, is the main component.

Since the boiling points for the chlorosilane mixture are so close, long distillation columns and careful distillation techniques are required to isolate the dimethyldichlorosilane.

2.1.2 Dimethyldichlorosilane hydrolysis
Because the Si-Cl bond is highly polarized and prone to nucleophilic attack, hydrolysis of dimethyldichlorosilane yields low molecular weight cyclic and linear siloxanes. In presence of water, the attack of both the Si-Cl bonds in dimethyldichlorosilane leads to the formation of a dimethyldisilanol, which is unstable and readily condenses, intermolecularly, to yield linear oligomers. Small linears can also condense intramolecularly to yield cyclic oligomers:

\[
x \text{Me}_{2}\text{SiCl}_2 \xrightarrow{-\text{HCl}} x \text{Me}_2\text{Si(OH)}_2 \xrightarrow{-\text{H}_2\text{O}} \ldots \text{Me}_2\text{Si(OH)}_2 \xrightarrow{-\text{H}_2\text{O}} y \text{HO(Me}_2\text{SiO})_n \xrightarrow{-\text{HCl}} z \text{(Me}_2\text{SiO})_m
\]

Note: HCl released is recycled by reaction with methanol to produce the methyl chloride used in the first step.
2.1.3 Octamethyltricyclosiloxane polymerization

Highly pure octamethyltricyclosiloxane, \((\text{Me}_2\text{SiO})_4\) [4], can be isolated through distillation, therefore, it is typically used (rather than linears) in the production of silicone polymers for pharmaceutical applications. The ring opening polymerization is catalyzed by bases, e.g. KOH, to yield hydroxy terminated PDMS:

\[
x (\text{Me}_2\text{SiO})_4 + \text{KOH} \rightarrow \text{Me}_3\text{SiOSiMe}_3 + x (\text{Me}_2\text{SiO})_4
\]

After reaction, KOH can be neutralized with CO\(_2\) (to form K\(_2\)CO\(_3\)) and eliminated through filtration.

When the polymerization is conducted in the presence of hexamethyldisiloxane [5], which acts as a chain endblocker, trimethylsilyloxy-terminated polymers [6] are produced:

\[
\text{Me}_3\text{SiOSiMe}_3 + x (\text{Me}_2\text{SiO})_4 \rightarrow \text{Me}_3\text{SiO} (\text{Me}_2\text{SiO})_p \text{SiMe}
\]

or in the presence of divinyltetramethyldisiloxane [7], vinyldimethylsilyloxy terminated polymers [8] are produced:

\[
\text{ViMe}_2\text{SiOSiMe}_2\text{Vi} + x (\text{Me}_2\text{SiO})_4 \rightarrow \text{ViMe}_2\text{SiO} (\text{Me}_2\text{SiO})_p \text{SiMe}_2\text{Vi}
\]

The above polymers display a distribution of molecular weight around an average mass, depending on the amount of chain endblocker used in their production. Moreover, all these reactions are equilibrium reactions during which a certain quantity of oligomers, e.g. cyclics, is formed. Although volatiles can be removed under vacuum at elevated temperatures, a certain level of residual volatile oligomers may remain.

Thus, highly pure siloxane polymers can be produced if: highly reactive starting monomers, such as dimethylchlorosilane [1], are used and purified by distillation; cyclic siloxanes, such as octamethyltricyclosiloxane [4], are isolated from the hydrolizate by distillation prior to polymerization; neither organic solvents or heavy metals are used; and strong bases or strong acids which can be easily eliminated are used to catalyze the polymerization reaction.

Other siloxane copolymers, such as or polydimethyl-methylhydrogen siloxane [9], can be produced by using oligomers that are substituted by groups other than methyl:

\[
\text{Me}_3\text{SiOSiMe}_3 + x (\text{Me}_2\text{SiO})_4 + \text{Me}_3\text{SiO} (\text{MeHSiO})_p \text{SiMe}_3
\]

The addition reaction shown above utilizes catalytic concentrations of a platinum complex (5 - 20 ppm as Pt) and does not generate any by-products, hence it has advantages in pharmaceutical applications.\(^{(5)}\) Using a polymer containing high levels of SiH functionality allows for several vinyl endblocked chains to be crosslinked together. Based on this, a large number of commercial products are currently available as ready-to-use 2-part elastomers. Usually, the part A contains the vinyl endblocked polymer and the part B contains the vinyl endblocked polymer and the polymer containing high levels of SiH functionality.

These 2 part systems are stored separately prior to use and the crosslinking reaction is only initiated once parts A and B are mixed at defined ratio, usually 50:50. The reaction often occurs at room temperature; however, it can be heat accelerated to crosslink the elastomer in a few minutes after extrusion, injection or molding. Heat curable 1-part materials have also been developed;

2.2 Cross-linked Silicone Elastomers

PDMS polymers are very flexible with a very low glass transition temperature \((T_g = 146 \text{ K})\)\(^{(4)}\) and are easily crosslinked into 3-dimensional networks or elastomers by the formation of covalent bonds between adjacent chains.\(^{(1)}\) Different crosslinking reactions can be used: condensation with or without by-product liberation, peroxide initiated (with formation of peroxide by-products). For pharmaceutical applications, crosslinking by addition is preferred using vinyl endblocked polymers \(^{(8)}\) and polymers (or crosslinkers) containing high levels of SiH functionality \(^{(9)}\) as shown below:

where \(\text{---}\) represents the remaining part of the polymer and the other Si valences.

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however, although these 1-part products may reduce handling prior to use (no mixing), they have very limited shelf lives.

Since platinum catalysts can be poisoned by many nucleophilic substances, precautions should be taken to avoid contaminants such as amines or sulphur compounds (containers, gloves, etc.) which could form stable complexes with platinum, inactivate its catalytic effects and lead to cure inhibition of the addition crosslinking reaction.

Silicone elastomer properties are strongly dependent on both the polymer structure and the crosslinker used. Hard elastomers are produced when the cross-linking density is high. Conversely, elastomers with low crosslink densities produce soft, more plastic elastomers. Elastomers with higher mechanical strength can be produced by incorporating amorphous silica with a high specific surface area in their formulation.

Other ingredients, such as alcohols capable of reacting with SiH groups to liberate hydrogen:

\[ \text{ROH} + \text{HSi} \rightarrow \text{ROSi} + \text{H}_2 \]

can be incorporated into elastomeric formulations. Since this reaction is catalyzed by the same platinum complex as the addition reaction, both the hydrogen evolution and cross-linking reactions take place simultaneously leading to the formation of silicone elastomeric foams. This technology is currently used to cast silicone foam dressings for deep cavity wounds.

### 2.3 Silicone Pressure Sensitive Adhesives

The major components used to produce silicone fluids, gums and elastomers are reactive and/or non-reactive linear, di-functional, D, siloxane polymer units. When tri-functional, T, or quadra-functional, Q, units are included in the hydrolysis reaction, three-dimensional silicate networks are formed. This is demonstrated below for the hydrolysis of methyldichlorosilane in the presence of trimethylchlorosilane which yields:

\[
x \text{Me}_3\text{SiCl} + y \text{MeSiCl}_3 + \text{H}_2\text{O} \rightarrow z \text{Me}_3\text{Si} \cdot \text{O} \cdot \text{Si} \cdot \text{Me}_3 + \text{HCl}
\]

or \((\text{Me}_3\text{SiO}_{1/2})_x(\text{MeSiO}_{3/2})_y \) or \(M_xT_y\). The average molecular weight depends upon the amount of mono, M, units from the trimethylchlorosilane which act as endblocker and limit the growth of the resin molecule. Most of the resins are prepared in solvents and typically contain some residual hydroxy groups that can be further reacted to form a continuous network or varnish.

Silicone pressure sensitive adhesives have been produced by reacting silanol groups from silicate resin with hydroxy terminated PDMS in presence of ammonia as catalyst according to :(7)
3.0 Physico-Chemical Properties

3.1 Intramolecular interactions

PDMS polymers are characterized by strong chemical bonds, not easily broken by homolytic scission because of their polarity. Only strong acids or strong bases are capable to depolymerise the siloxane chain. As a result, the PDMS polymers are not very susceptible to oxidation or thermal degradation and they can be sterilized by heat.

While the siloxane backbone is made of very polar Si-O bonds, the PDMS polymers are actually very hydrophobic as the methyl groups shield the polar backbone, a feature enhanced by the very low energy of rotation around a Me2Si - O bond (rotation barrier = 3.3 kJ/mol) which allow PDMS polymers to reduce their surface energy and their surface tension by exposing a maximum number of methyl groups. The PDMS low surface tension property is used to prepare antifoam agents.

3.2 Intermolecular interactions

Because of its low rigidity, the siloxane backbone allows the methyl groups to be easily exposed to the outside and as a result, the PDMS polymers are characterized by low intermolecular interactions. This is demonstrated in several ways:

- even at high molecular weight, the PDMS polymers are liquid;
- the PDMS polymers properties are not very temperature dependent;
- the PDMS polymers, compared to other polymers, are very permeable to the diffusion of various substances, gases or active drugs (table 2).

Table 2: Comparison of the PDMS permeability with other polymers.

<table>
<thead>
<tr>
<th>Type</th>
<th>Permeability to O₂ (cm³.cm)/(s.cm².kPa) x 10⁻⁷</th>
<th>Permeability to CO₂ (cm³.cm)/(s.cm².kPa) x 10⁻⁷</th>
<th>Relative permeability to Progesterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polydimethylsiloxane</td>
<td>79</td>
<td>405</td>
<td>100</td>
</tr>
<tr>
<td>Polyethylene</td>
<td>0.002</td>
<td>0.007</td>
<td>0.1</td>
</tr>
<tr>
<td>Polytetrafluoroethylene</td>
<td>0.001</td>
<td>0.003</td>
<td>0.1</td>
</tr>
</tbody>
</table>

4.0 Toxicology

As described in the previous sections, silicones are used in a wide variety of applications.

These silicones include low molecular weight linear and cyclic volatile oligomers or volatile methyl siloxanes as well as polydimethylsiloxane (PDMS) polymers with viscosities ranging from 10 to 100,000 cSt or higher.

Volatile methyl siloxanes (VMS) like cyclic siloxanes, (SiMe₂O)ₙ, are widely used in skin care products, in particular the four (n = 4) and five (n = 5) member cycles referred to as D₄ and D₅, respectively. Extensive safety studies conducted on D₄ and D₅ have indicated effects that appear to be rat specific and, therefore, pose little or no risk to human health. The effects observed with D₄ include a reduction in litter size and in the number of implantation sites in the uterus and an increase in uterine endometrial hyperplasia and adenomas. The fertility effects and uterine adenomas occur at the highest vapor exposure concentration achievable without formation of an aerosol (i.e., 700 ppm) and by modes of action that appear to be rat specific. Exposure to D₅ at the highest achievable vapor concentration of 160 ppm caused an increase in uterine endometrial adenocarcinomas that is presumed to occur by a rat-specific mode of action like D₄. Both D₄ and D₅ cause a non-adverse, adaptive increase in liver weight that is considered phenobarbital-like. Neither of these materials are mutagenic or genotoxic nor are they immunotoxic. Typically, D₄ and D₅ show around 0.5% and 0.05% dermal absorption, respectively. Following dermal absorption, >80% of D₄ and >90% of D₅ is eliminated in expired air within 24 hours of exposure.

The lowest molecular weight linear material is the highly volatile hexamethyldisiloxane, Me₃SiOSiMe₃ (HMDS). HMDS has generally shown no significant toxicity. However, recent data have indicated an earlier incidence of testicular tumors in male rats exposed to high levels of material via inhalation. In this same study, there was also an increase in the incidence of kidney tumors in male rats, which have been shown to be mediated through a protein, 2u-globulin, which is specific to male rats. Other linear molecules of three, four, or five siloxane units have not exhibited hazards in studies to date, though the data are limited for long-term exposure. The materials have very limited absorption via typical exposure routes. Like the higher molecular weight polymers, the low molecular weight linear PDMS materials are not mutagenic, irritating or acutely toxic.

The most widely used silicones are the trimethylsiloxy end-blocked PDMS polymers, Me₃SiO(SiMe₂O)ₙSiMe₃, with viscosities between 10 to 100,000 cSt. These materials have shown no toxicity during administration via typical exposure routes, which are either oral or dermal. Due to their high molecular weight, they are neither absorbed from the gastrointestinal tract nor through the skin. Following oral ingestion, PDMS is excreted in the feces without modification. In vitro studies have not indicated mutagenic or genotoxic effects. Repeated oral or dermal dosages of different viscosities demon-
strated no adverse effects to a variety of mammalian species. Inhalation of aerosols of oily or fatty-type materials, including some kinds of silicones, into alveolar regions of the lung may result in acute toxicity that is likely related to physical disturbances of the lining of the lung with associated effects. There is no evidence of reproductive or teratogenic effects of PDMS from studies conducted with rats or rabbits. Overall, these data show no hazard of PDMS to humans.28

5.0 Biocompatibility
The innocuity of silicones leads to their use in applications where prolonged contact with the human body is involved: textile fabrics, cosmetics, food contact and medical applications. Silicone elastomers are used in many class II or III medical devices regulated by the European Medical Devices Directive such as tubing for extra-corporeal circulation used during cardiac surgery, hydrocephalic shunts and pacemakers leads. Their excellent biocompatibility is partly due to the low chemical reactivity displayed by silicones, their low surface energy and their hydrophobicity.14

6. Epidemiology
With the resolution of the legal controversy regarding silicone gel-filled breast implants well underway, these medical devices remain available with some restriction in the U.S., where they have been used since the early 1960s. Outside of the U.S. and Canada, however, access to these devices is unconstrained. The controversy in the 1990s initially involved breast cancer, then evolved to autoimmune and connective tissue disease, and continued to evolve to the frequency of local or surgical complications such as rupture, infection or capsular contracture. Epidemiology studies have consistently found no association between breast implants and breast cancer.18-24 In fact, some studies suggest that women with implants may have decreased risk of breast cancer.22, 23 Reports of cancer at sites other than breast are inconsistent or attributed to lifestyle factors.25 The research on autoimmune or connective tissue disease has also been remarkably uniform and concludes there is no causal association between breast implants and connective tissue disease.26-31

7.0 Impact on the Environment
A large number of studies have been conducted to evaluate the fate and effects of silicones in the environment throughout their life cycle.45 Releases to the environment from the manufacture of polydimethylsiloxane (PDMS) are strictly controlled and must comply with emission limits specified by regulatory authorities. Subsequently, the environmental fate of silicones depends to a large extent on the nature of the application, the physical form of the material and the method of disposal. Low molecular weight PDMS polymers (< 1000 Da) are primarily used in personal and household care products. High molecular weight PDMS polymers are important as anti-foams and lubricants for domestic and industrial use. However, a more important application is as a “solid” silicone such as PDMS-based rubbers or sealants, both of which may be used either in the home (e.g., bath sealants, bake-ware or baby teats) or diverse industrial applications such as textile coatings, electronics, silicone moldings and rubber gaskets.

“Solid” silicones enter the environment as a component of domestic or industrial waste and will be either land filled or incinerated. In the latter case, they are converted back to inorganic ingredients, amorphous silica, carbon dioxide and water vapor. “Liquid” silicones, both high and low molecular weights, which are used in rinse-off products such as shampoos, hair conditioners or silicone antifoams in detergents, become part of municipal wastewater. The same is true for PDMS used as antiflatalents in pharmaceuticals. High molecular weight silicones, are virtually insoluble in water, thus, as a consequence of their high binding potential for organic matter, they are effectively removed from municipal wastewater onto the sludge during wastewater treatment. Extensive studies show that more than 95% of silicones are removed from effluents in this way, and that the concentration in discharged effluents borders the level of detection (5 μg/l).46,47

The subsequent fate of silicones depends on the fate of the sludge. If incinerated, silicones degrade as indicated above. The other principal outlet for sludge is use as a soil conditioner or amendment. In small-scale field studies, the application of sewage sludge-bound PDMS to soil caused no observed adverse effects on crop growth or soil organisms.4 Little or no uptake into the plants was observed, which is consistent with animal studies showing that high molecular weight PDMS is too large to pass through biological membranes of either plants or animals. Extensive studies ranging from small-scale laboratory tests to field studies show that sewage-sludge bound PDMS degrades in soils as a result of contact with clay minerals.48-54 The clay acts as a catalyst to depolymerise the siloxane backbone.53,54 The primary degradation product, regardless of the PDMS molecular weight, is dimethylsilanediol, Me2Si(OH)2.50 Depending on the soil type, this undergoes further degradation either in the soil via biodegradation or evaporates into the atmosphere, where it degrades oxidatively via reaction with hydroxyl radicals.55-58 Whether degradation occurs in the soil or in the air, there is conversion to inorganic constituents, amorphous silica, carbon dioxide and water.
8. Conclusion
Polydimethylsiloxanes are formed from compounds that are largely available: sand and methanol. Often referred to as silicones, they are used in many health care applications because of their stability, low surface tension and lack of toxicity. Methyl group substitution or introduction of tri- or tetra-functional siloxane units leads to a wide range of structures. Polymers can be easily cross-linked at room or elevated temperature to produce cured elastomers that maintain many of the same characteristics as the uncured polymers. These factors help explain the commercial success of silicones and should support their future use in and development for products targeted for the pharmaceutical market.

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9. References
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