# PROCESSING SILICONE POLYMERS: A FOUNDATION FOR CREATING CONSISTENT SILICONE SYSTEMS

**Kyle Rhodes**
NuSil Silicone Technology – Europe
2740 route des Crêtes, BP 325
06906 SOPHIA ANTIPOLIS cedex, France
Tel: 011.33.(0)4.92.96.93.31
Fax: 011.33.(0)4.92.96.06.37
Kyler@nusil.com

**Stephen Bruner**
NuSil Technology
1050 Cindy Lane
Carpinteria,  California 93013 USA
Steveb@nusil.com

**Biographical Note:**

Kyle Rhodes has a Master's Degree in Polymer Chemistry, and is the General Manager for NuSil Technology Europe located in Sophia Antipolis, France.  Previously at NuSil, Kyle was responsible for direct customer sales in the eastern United States, and then managed the European Sales for NuSil Technology in the Medical Device, Aerospace, Optics, and Electronic sectors through various distributors in Europe and the Middle East. Prior to NuSil, Kyle has spent time as an R&D Chemist, Quality Manager, Applications Engineer, and Senior Technical Sales for a UV curable adhesive company.



Stephen Bruner is the Marketing Director at NuSil Technology.  He has been at NuSil for 12 years.  Steve has a bachelor's degree in Chemistry from the University of Colorado and a Masters in Business Administration from Pepperdine University

**Abstract:**

The unique chemistry of silicone polymers are customizable to create a variety of material types with a specific properties. The polymer properties have proved useful in a number of applications, including drug delivery. Silicone polymers represent the basis of all silicone systems, adhesives, gels, elastomers, and resins. Silicone polymers are created via acid or base catalyzed polymerizations of silicone cyclics and endblocking silicone molecules. The polymerization process is an equilibrium reaction that yields both starting materials and a polymer distribution of varying molecular weight. The subsequent processing and testing of these polymers is critical to their performance in silicone systems. Lack of proper processing may lead to variable physical properties in elastomer systems. These variations may, in turn, affect the system's function in drug delivery systems, influencing factors like drug permeation rates. The paper critically evaluates the polymerization process and subsequent purification processes that are critical to producing consistent silicone systems.

**Introduction:**

*Silicones in medical device applications*

Silicones expanded into healthcare and medical applications in the 1950's after extensive use in the aerospace industry in the previous decade. Within a twenty years, a considerable body of work had established that silicone oils and crosslinked siloxane systems did not give rise to harmful consequences when subcutaneous, intracutaneous, and intramuscular administrations were performed. In 1954, J.D.B. McDougall reported the cultures of various tissues of warm blooded animals, which are known to be extraordinarily sensitive to foreign influences, show no deviation from the usual growth picture on contact with liquid, semisolid, and rubberlike silicone products (1). Silicones have been characterized as biologically and toxologically inert as a result of this work. (2). Many applications such as pacemaker leads, hydrocephalus shunts, heart valves, finger joints and intraocular lenses utilize silicone materials.

*Silicones in drug delivery applications*

The interest in silicones from the pharmaceutical perspective is a changing landscape. Simethicones are active pharmaceutical ingredients known for their defoaming (or anti-gas) properties and have existed for over 30 years. Likewise - silicone tubing used in the delivery of pharmaceutical compounds is not a novel concept. What is new is the development of drug delivery systems that exploit the properties of silicone materials. Transdermal drug delivery systems, transmucosal and implanted drug delivery systems are examples of products that are in transition. Commercial applications such as Norplant (http://norplantinfo.com) and Femring (http://www.femring.com) are examples clinically successful drug delivery applications that involve silicone materials. Patent number 6,039,964 cites a number of agents that could be used in a drug eluting applications. The drug cited included antidepressants, anxiolytics, vitamins B6, D, and E, antifungal, opioid analgesics, non-opioid analgesics, and antiviral compounds. Pharmaceutical based coatings for medical devices are yet another area of development.

*Polysiloxane Chemistry*

The term "Silicone" is actually a misnomer. Normally the suffix '-one' delineates a substance has a double bonded atom of oxygen in its backbone. Scientists initially believed that silicone materials contained double bonded oxygen, hence the use of 'silicone.' However, silicones are really inorganic polymers, having no carbon atoms in the backbone, and therefore should be named 'Polysiloxanes.' Figure 1 below shows their typical structure:
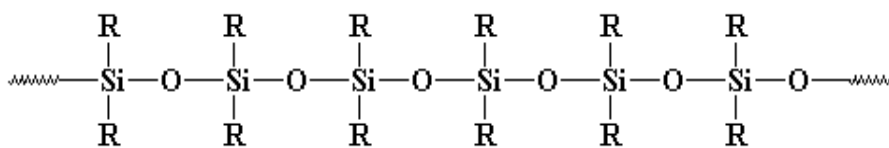
Figure 1. Silicone polymer backbone. R=$CH_3$, phenyl (aromatic carbon ring), $F_3CCH_2CH_2$, $CH=CH_2$

This structure allows polysiloxanes to be used in a wide array of applications because different types of constituent groups can be incorporated onto the polymer. Different polysiloxanes can provide a variety of excellent elastomeric properties that can be chosen according to a specific use. Various types of silicones, or polysiloxanes, and their property advantages include:

*Dimethyl silicones*, or dimethylpolysiloxanes, are the most common silicone polymers used industrially. These types of polymers are typically the most cost effective to produce and generally yield good physical properties in silicone elastomers and gels. The polymer pictured below contains vinyl endgroups that participate in a platinum catalyzed addition reaction (see section on *Cure Chemistry* for more information).
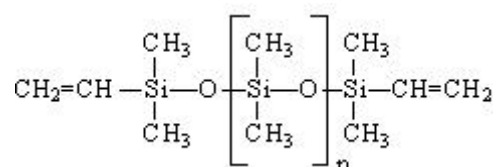


*Methyl phenyl silicone* systems contain diphenyldimethylpolysiloxane co-polymers. The steric hinderance of the large phenyl groups prohibit significantly high concentrations of diphenyl units on the polymer chain. The phenyl functionality boosts the refractive index of the polymers and silicone systems that use these polymers. Silicone polymers with diphenyl functionality are useful in bio-photonic applications (e.g., intraocular lenses) where higher refractive index materials can be useful in creating a thin lens. Creating devices with several layers of diphenyl elastomer systems may be useful in controlling release rates of certain drugs. The diagram below shows a typical structure for a methyl phenyl silicone:
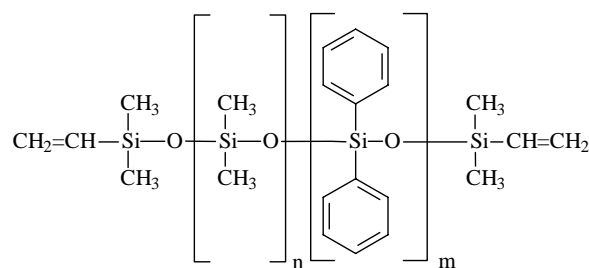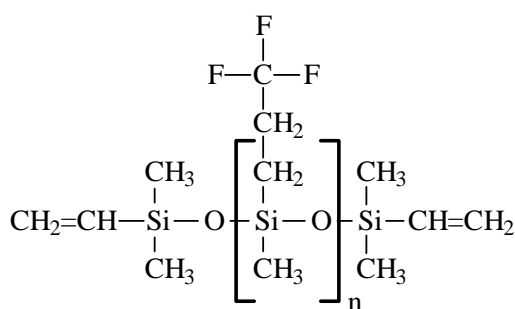


Figure 2.

*Fluorosilicones* are based on trifluoropropyl methyl polysiloxane polymers and used for applications that require fuel or hydrocarbon resistance. The trifluoropropyl group contributes a slight polarity to the polymer, resulting in swell resistance to gasoline and jet fuels. However, polar solvents such as methyl ethyl ketone and methyl isobutyl ketone may significantly affect fluorosilicones. While some fluorosilicones contain 100% trifluoropropylmethylpolysiloxane repeating units, other systems contain a combination of the fluorosiloxane units and dimethyl units to form a co-polymer. Adjusting the amount of trifluoropropyl methyl siloxane units in the polymerization phase provides optimal performance in specific applications. The diagram below shows a typical structure for a fluorosilicone:

$$\text{CH}_2{=}\text{CH}-\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{Si}}}-\text{O}\left[\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\overset{\overset{\overset{\overset{F}{|}}{F-C-F}}{|}}{\text{CH}_2}}{|}}{\underset{|}{\text{CH}_2}}{\text{Si}}}-\text{O}\right]_n\underset{\underset{\text{CH}_3}{|}}{\overset{\overset{\text{CH}_3}{|}}{\text{Si}}}-\text{CH}{=}\text{CH}_2$$

*Silicone Material*                                             *Compositions:*

*Silicone Fluids:*

Fluids are non-reactive silicone polymers and can be formulated with dimethyl, methylphenyl, diphenyl, trifluoropropylmethyl functionality. The viscosity of these materials depends largely on the polymer's molecular weight and steric hinderance of functional groups on the polymer chain. Fluids are typically used in lubrication and dampening applications.

*Silicone Gels:*

Silicone gels are composed of reactive silicone polymers and reactive silicone crosslinkers. These materials are designed to have a very soft and compliant feel when cured. Typical applications include tissue simulation and dampening.

*Silicone Pressure Sensitive Adhesives:*

Silicone PSA's are composed of polymers and resins. These materials are designed to perform in an uncured state . PSA's form a non-permanent bond with substrates such as metals, plastics, glass, and skin.

*Silicone Elastomers:*

Silicone elastomers fall into several categories: High consistency rubbers, liquid silicone rubbers, low consistency elastomers and adhesives.

*High consistency elastomers* are typically composed of high viscosity polymers, high levels of reinforcing silica, and some contain crosslinking polymers. These materials are clay like in an uncured consistency and offer good physical properties. High consistency materials can be molded into parts by compression molding or extruded into tubing configurations.

*Liquid silicone rubbers* or LSR's are elastomers that contain medium viscosity polymers and moderate amounts of silica. The cured elastomers have good physical properties. They tend to have an uncured consistency like that of Vaseline. These materials can be molded into parts and require the use of liquid injection molding equipment.

*Low consistency silicones* are pourable systems that are composed of lower viscosity polymers and reinforcing fillers such as silica and resin. These systems have lower physical properties than high consistency or LSR formulations but can easily be processed and molded by hand. These materials can be molded into parts by compression molding or can be used as cured in place seals or gaskets.

*Adhesives* are low consistency elastomers that contain lower viscosity polymers, reinforcing silica and adhesion promoters. Silicone adhesives are designed to adhere silicones to various substrate surfaces including metals, glass and certain plastics.

*Cure Chemistry*

Silicone systems can be cured by platinum catalyzed addition cured systems, tin condensation cure systems, peroxide cure systems and oxime cure systems. Some of the oldest cure chemistry in silicones is acetoxy tin condensation cure system such as those used in household bathroom caulk. These systems yield a vinegar smell as acetic acid is a byproduct of the reaction. For the purposes of our discussion, we will focus on platinum systems, tin condensation systems, as they are the most prevalent in drug delivery type applications.

Platinum catalyzed silicones utilize a platinum complex to participate in a reaction between a hydride functional siloxane polymer and a vinyl functional siloxane polymer. The result is an ethyl bridge between the two polymers. The reaction mechanism is pictured below:
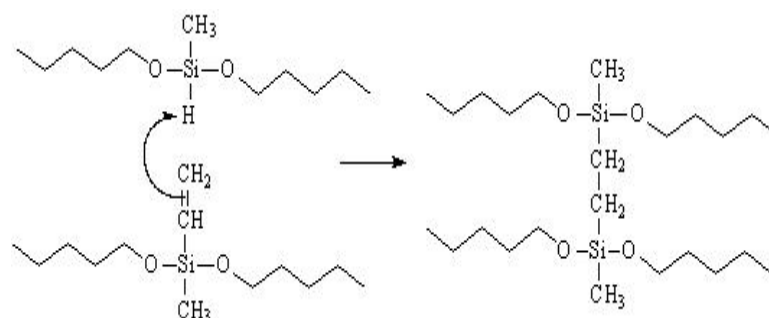


Platinum systems are often cured quickly with heat but can be formulated to cure at low temperatures and room temperature if necessary. The advantages of these systems include fast cure and no volatile byproducts. Cure inhibition is a disadvantage of this cure system. Inhibition is defined as either temporarily or permanently preventing the system from curing. Some types of inhibitors are added to these systems to control the rate of cure but contact with tin, sulfur, and some amine containing compounds may permanently inhibit cure. Compounds that inhibit cure can be identified easily by attempting to cure a platinum catalyzed system in contact with the compound. Inhibition results in uncatalyzed regions of elastomer systems or inconsistency in cure over time.

Tin condensation systems involve hydroxyl functional polymers and alkoxy-functional crosslinking compounds. The alkoxy functional crosslinker first undergoes a hydrolysis step and is left with a hydroxyl group. This hydroxyl group then participates in a condensation reaction with another hydroxyl group attached to the polymer. The reaction can proceed without the assistance of the tin catalyst, but the presence of the catalyst boosts the rate of reaction. The reaction mechanism is pictured below:
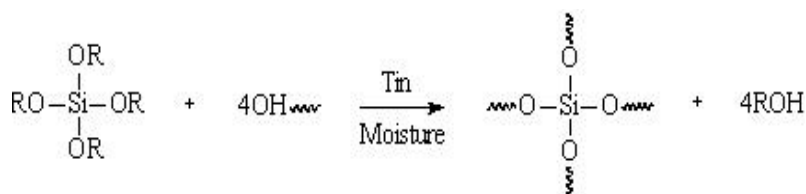


The advantages of using condensation systems is that they cure at room temperature (useful for temperature sensitive additives) and have robust cure systems that are difficult to inhibit. The disadvantages of condensation systems is the time it takes to cure the elastomer system, often seven days is required for a complete cure.

## Discussion

*Silicone Polymerizations:*
Commercial production of silicone polymers often begins with polysiloxane cyclic and short-chained siloxane oligmers, typically derived from the hydrolysis of chlorosilane monomers. While creating many specialized functional polymers and silicone resins begins with chlorosilane chemistry, this paper focuses on building polymers from the cyclic stage.

Polysiloxane cyclics can convert to high molecular weight polymers at temperatures of 250°C to 300°C in closed systems. Thermal degradation of organic constituents on the silicon atom can create undesirable crosslinking, essentially forming non-linear structures. To achieve any appreciable amount of high molecular weight species, applying pressures of 1000 to 7000 kg/cm$^2$ is required. Fortunately, more commercially viable options, such as the use of catalysts, can polymerize polysiloxane cyclics into linear, high molecular weight silicones at considerably lower temperatures and pressures.
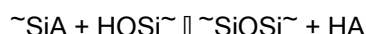
Here we show an example of octamethyltetracyclosiloxane as the cyclic for the discussion. This molecule (pictured below) is very reactive when compared to other organosiloxane compounds such as diphenylsiloxane cyclics, because of the relatively uninhibited access of a catalyst to the siloxane oxygen.
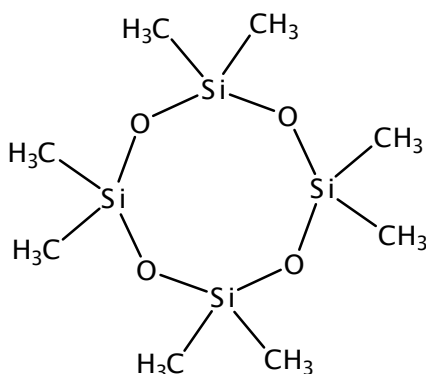


Polymerizations can be catalyzed with either Brönsted or Lewis acids. The acid proton attacks the lone pairs of the siloxane oxygen, creating a scission (acidolysis) at the oxygen and silicon bond:

$$HA + (R_2SiO)_n \rightarrow HOSiR_2(OSiR_2)_{n-1} A$$
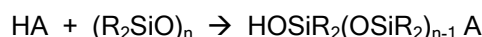
This new ionic species may react with other similar species forming a siloxane bond. Other scenarios include the condensation of the two hydroxy functional siloxane units and the hydrolysis of the cation end of the polymer (all three scenarios are depicted below):

$$\sim SiOH + HA \quad \sim SiA + H_2O$$

$$\sim SiA + HOSi\sim \quad \sim SiOSi\sim + HA$$

$$\sim SiOH + HOSi\sim \quad \sim SiOSi\sim + H_2O$$

According to Noll (2), there is an energy gradient that favors macromolecules in these situations.

Using alkaline catalysts is another method of catalyzing a siloxane polymerization. The reaction proceeds differently than the Lewis acid catalysis. The base attaches itself to the silicon atom in the polysiloxane, cleaving the bond as shown below:
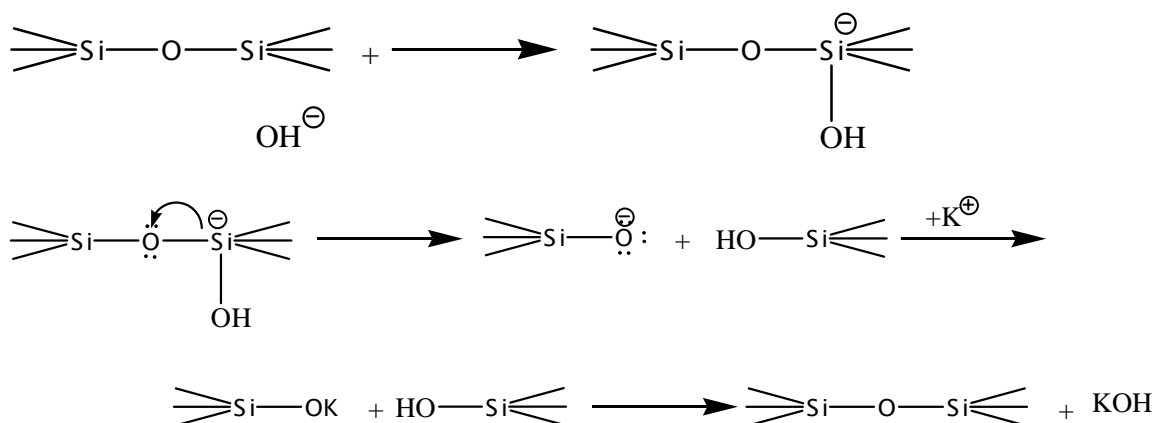


Both reactions are equilibrium reactions, and in the presence of an end blocking or chain terminating species such as hexamethyldisiloxane, the reaction begins with an increase in viscosity.

This increase in viscosity occurs primarily because the rate of cyclic opening and polymerizations is greater than that of the end blocking molecule scission. The polymer chain forms and breaks through the course of the reaction. Typical reactions take several hours to reach equilibrium. In the case of polymerizations involving octomethyltetracyclosiloxane and hexamethyldisiloxane, an equilibrium mixture of roughly 85% linear polymers and 15% cyclics is present. The stoiciometric amounts of cyclics and chain terminating

species in the reaction determines the molecular weight of the polymer . Small amounts of endblocking species create larger linear polymers, and conversely, large amounts of those species result in shorter, lower molecular weight polymers. After equilibrium, purging acid catalysts from the system stops the reaction, and elevated temperatures or carbon dioxide can deactivate alkaline catalysts.

As stated above, the product of the polymerization reaction is a mixture of cyclics, short chained linear molecules and higher molecular weight polymers. The length of the polymers, or molecular weight, is normally distributed, and gel permeation chromatography will show a bimodal distribution with a smaller, low molecular weight peak (representing cyclics and very short chained linears) and a larger peak representing the larger molecular weight polymers.
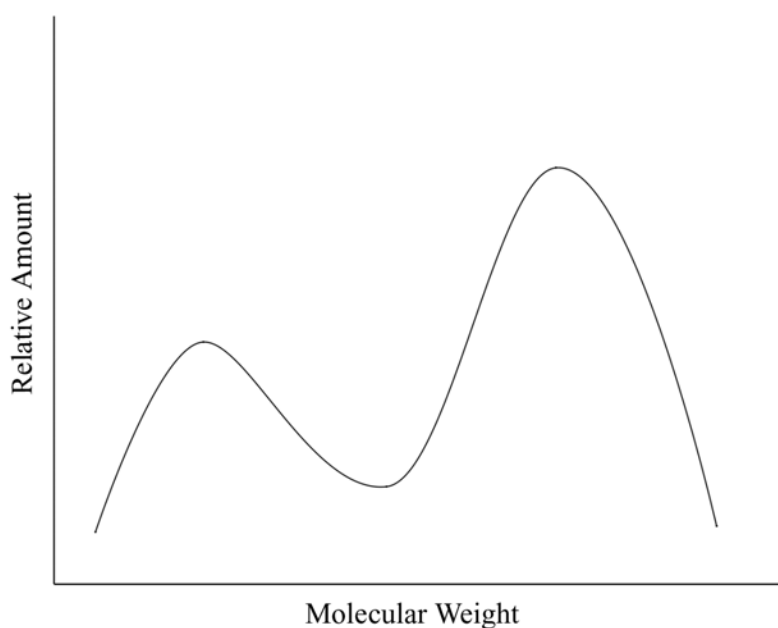


The species represented in the smaller peak and the lower molecular weight portion of the larger peak may readily migrate out of a cured elastomeric matrix if the species lacks the proper reactive groups to tie in. Another scenario involves the shortchained reactive species which may prove problematic to achieving consistent crosslink density if not controlled. Removal of these species is detailed in the sections below.

*Processing:*

*Wiped film evaporator operations*
Wiped film evaporation can process silicone materials utilizing polymers with viscosities under 500,000 cps. Most formulations of liquid silicone elastomer systems contain polymers of this size. Polymers or materials with viscosities higher than this amount typically require a process called solvent extraction. These materials are typically high consistency rubbers or pressure sensitive adhesives (PSAs).

A distillation process known as wiped film evaporation can remove low molecular weight fractions of polymerizations. The wiped film apparatus is typically an evacuated chamber with heated walls and a central cooling finger designed for condensing low molecular weight molecules. After the polymerization reaction is complete, the material is driven into the heated chamber and wiped onto the heated chamber walls. This exposes a thin film of the polymerization to heat under vacuum conditions. Higher molecular weight silicones continue to migrate down (or wipe down) the chamber wall, while the low molecular silicones condense on the cold finger and are routed to a collection vessel.

*Solvent Washing Technique:*
As stated above, making a silicone polymer via an equilibrium method, a portion of monomer remains and a population of short-chained oligomers forms in addition to the main product. This portion varies depending on the type of siloxane polymer and constitutes the volatile condensable material. These volatile condensable materials are the specific moieties that need to be removed to produce a low outgassing

material. If not removed, they will separate from the main polymer and contaminate the surrounding environment, leaving a silicone residue.

When the polymer in question is of larger molecular weight, such as those in a PSA, it can be difficult to remove the volatile condensable materials by the conventional stripping methods. A solvent washing technique is used instead. Essentially, solvent washing is a form of extraction involving multiple solvents with varying solvating abilities. Due to the nature of the polymer prior to extraction, a second solvent immiscible with a bulk polymer but miscible with the first solvent is used to remove low molecular weight volatile condensable material. In addition, it is difficult to perform a simple single solvent exaction due to the high molecular weight of the polymer. The multiple solvent method allows the extractant to reach and solvate this lower molecular weight fraction and remove it from the bulk. The washing process may need to be repeated several times, dependent again on the type of siloxane polymer involved.

*Siloxane Chemistry as it relates to drug delivery applications*

*Structure and Applications*

For the purposes of the article, the drug delivery systems presently discussed utilize the permeation characteristics of silicones in the delivery of the pharmaceutical agents. As was mentioned above, device configurations can range from reservoir designs to drug in elastomeric matrix. Both designs are cited in transdermal, transmucosal and implanted drug delivery designs. The key to these designs is the permeation of drugs and specifically the rate in which the agent permeates. Permeability of active agents is dependent on two key factors, solubility and diffusivity.

*Solubility*

The siloxane polymer backbone of repeating silicon and oxygen atoms creates a potential for interaction. The two free pairs of electrons associated with each oxygen atom can form hydrogen bonds with proton donors. Silicone elastomer systems can be strengthened with silica or resin reinforcement, which form hydrogen bonds with the polymer backbones.

Despite the ability to form hydrogen bonds, silicone is considered hydrophobic in nature. The methyl constituency on the siloxane polymer backbone creates this effect. This is ideal for the solubility of lipophillic pharmaceutical agents having mostly non-polar structures with few alcohol or ketone groups. Below are the molecular structures for estradiol, levorphanol, and metrondiazole.



| Estradiol | Levorphanol | Metrondiazole |
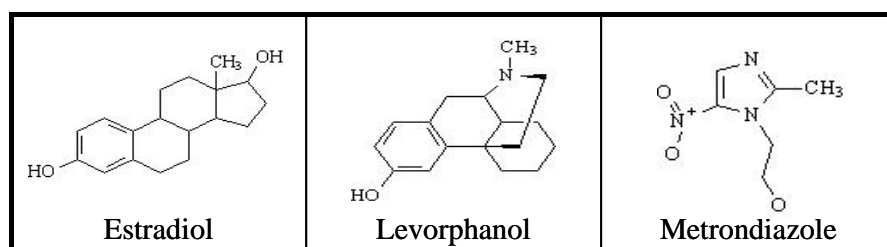
Additional work in this area has determined that the melting point of a molecule, or the energy of disassociation, can be used to determine the solubility of similar molecules in silicone materials (3). Other studies suggest the addition of polar groups onto an active agent can negatively impact the solubility of the agent in the silicone and in turn impact the permeability of that agent. (4)

It appears the interaction between the oxygen of the siloxane backbone does have some hydrogen bonding with the alcohol functionality of many active pharmaceutical agents. This is evidenced by a rise in release rates when a fatty acid ester is used in incorporated into the elastomer system. The molecular structure of Linoleic Acid is shown below:

$$CH_3CH_2(CH=CHCH_2)_3(CH_2)_5CH_2\overset{\overset{\displaystyle O}{\|}}{C}-OH$$
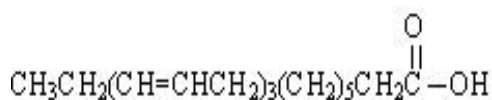
It is believed that fatty acid esters increase the hydrophobicity of the siloxane system (5). It can be speculated that the carboxylic acid group competes for siloxane oxygen, effectively "reducing" the concentration of siloxane oxygen available in the elastomer system.

The silicone polymer backbone can also be modified to improve the solubility of certain agents. Trifluoropropylmethylpolysiloxanes exhibit a slightly more polar characteristic and may improve the solubility of more hydrophillic active agents. Conversely, diphenyl functional siloxanes may improve solubility of more hydrophobic agents as the large phenyl groups provide steric hinderance of the oxygen on the siloxane backbone. Keep in mind that the modifications to the polymer may affect the second critical factor to drug permeability - diffusivity.

*Diffusivity*

The large atomic volume of the silicon atom, as well as the size and position of constituent groups, explain the virtually complete freedom of rotation around the Si-O-Si bond. Silicone polymers form helixes, and the bond angles of the silicon-oxygen bonds create large amounts of free volume in silicone elastomers. This free volume, and the high compressibility found in silicones, is associated with their permeability to gases and liquids. The gas permeability of silicone rubber is up to 100 times greater than natural or butyl rubber. Silicone rubbers swell in aliphatic, aromatic and chlorinated hydrocarbon solvents.

Silicone gaskets for industrial applications absorb lubricating oils and will tend to "wet" the surface of the elastomer system after the source of the lubrication is removed (2). NuSil Technology takes advantage of this phenomenon in our various self-lubricating elastomer formulations. Proprietary silicone fluids are incorporated into the elastomer formulation, and migrate to the surface of the molded component after cure.

The prevailing theory in this area is that the amount of free volume in an elastomer systems and the relative freedom of movement of the polymer chains is the prime determinant in the diffusivity of an active agent. Work in this area relates molecular weight and molecular volume to diffusivity rates, i.e., the larger the molecule the less diffusivity and consequently lower permeation rates (3). This work is supported by a separate study measuring average "mesh" size (a function of crosslink density) and diffusivity(6). In summary, it appears the size of the molecule, the amount of space in which to fit that molecule, and the relative freedom in which the molecule moves from space to space will have an impact on diffusivity and ultimately permeability.

When developing silicone based drug delivery systems, solubility and diffusivity, the two factors critical to permeability must be understood to determine if the active agent and silicone can produce the desired result. Should developers determine that the agent – silicone permeability is ideal, further modifications to the silicone system may produce optimal release rates.

## Conclusion:

Silicone materials enjoy considerable use in the healthcare and drug delivery industries because of their historic use in these sensitive applications. As outlined above, drug delivery applications are dependent on factors like solubility and diffusivity. Diffusivity itself relies on crosslink density to control permeability. Drug delivery applications that place very specific permeation demands on materials require consistency, and this begins with the silicone polymer synthesis and purification. Commercial polymerizations lead to a distribution of polymers and cyclics, and the lower molecular weight species need to be removed to produce consistent silicone products. The authors, on the basis or the information provided above, speculate consistent silicone materials will result in consistent drug permeability rates. Researchers have additional options when it comes to evaluating different levels of purification and may find benefit in fine tuning the consistency of drug permeation or adjusting to a specific permeation rate.

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(6)  Nabahi and Shorhre, U.S. Pat. 5,788,980 (August 4, 1998)