Silicones as a Material of Choice for Drug Delivery Applications

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Abstract

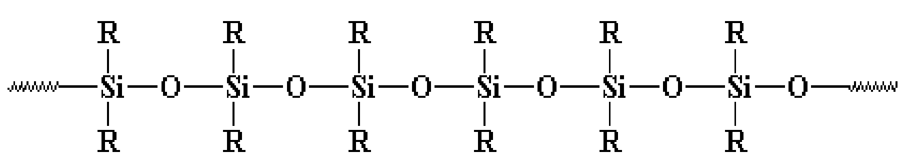
This paper will investigate the benefits of using silicone in drug delivery applications. This investigation first provides an overview of how versatile of a material silicone can be to the drug delivery industry. An examination of the chemistry of silicone, the multiple material composition options and various cure chemistries demonstrates how silicone can be tailored to fit specific drug delivery applications. Then, a general investigation of the way a silicone interacts with a drug, in regards to compatibility and potential interactions, exhibits silicone's ability to deliver pharmaceutical agents. The paper will also review factors that have made silicones the materials of choice in the medical device industry, particularly for long-term implantable devices. Examples of applications demonstrate the reasons for choosing silicone over a different material. The paper will finish with real world examples of current drug delivery applications incorporating a silicone, such as hormone replacement therapies, to manifest the benefits of using silicone in drug delivery applications.

Introductions

The chemistry behind silicone essentially equates to material versatility, and this versatility allows silicone materials to be custom designed to fit drug delivery applications. The polymer chemistry that constitutes silicones allows various types of silicone polymers, which each provide varying properties beneficial to different applications. Silicone chemistry also makes a diverse set of material compositions available for a broad range of applications. Finally, silicone cure chemistry provides options to optimize how a silicone can be used when applied to specific applications.

Polymer Chemistry

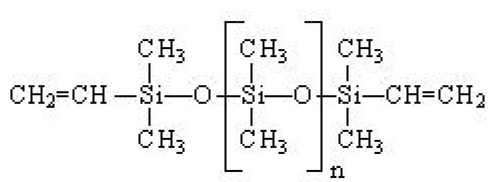
The term "Silicone" is actually a misnomer. Normally the suffix '-one' delineates a substance has a double bonded atom of oxygen in its backbone. Scientists initially believed that silicone materials contained double bonded oxygen, hence the use of 'silicone.' However, silicones are really inorganic polymers, having no carbon atoms in the backbone, and therefore should be named 'Polysiloxanes.' The diagram below shows their typical structure:



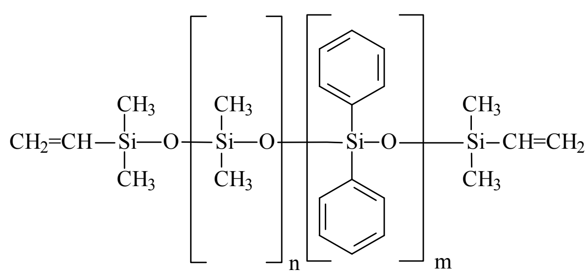
R=CH3, phenyl (aromatic carbon ring), F3CCH2CH2, CHCH2

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:

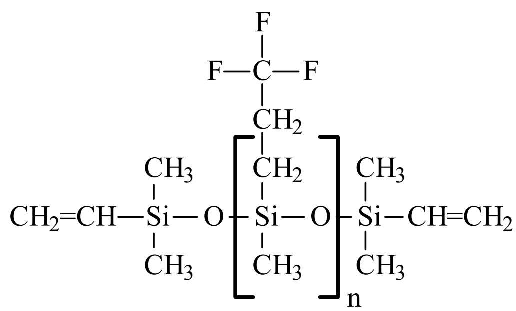
Dimethyl silicones, or dimethylpolysiloxanes, are the most common silicone polymers used industrially. These types of polymers are typically the most cost effective to produce and generally yield good physical properties in silicone elastomers and gels. The polymer pictured below contains vinyl endgroups 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:



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:



Material Composition

While the polymer chemistry and structure of silicone provide the different types of silicones outlined above, they also allow those different types of silicones to appear in a wide variety of material compositions. This broad range of material compositions makes silicone a viable option to endless numbers of healthcare and drug delivery applications. Some silicone material compositions and their typical applications include:

Silicone Fluids are non-reactive silicone polymers formulated with dimethyl, methylphenyl, diphenyl, or trifluoropropylmethyl constituent groups. These materials' viscosity depends largely on molecular weight of the polymer and steric hinderance of functional groups on the polymer chain. Fluids are typically used in lubrication and dampening applications.

Silicone Gels contain 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 (PSA's) contain 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 fall into several categories: high consistency, liquid silicone rubbers, low consistency elastomers, and adhesives.

High consistency elastomers typically contain high viscosity polymers and high levels of reinforcing silica. These materials are clay-like in consistency in their uncured state, and offer good physical properties when vulcanized. High consistency materials can be molded into parts by compression or transfer molding, and are most commonly used for extrusion to yield tubing configurations.

Liquid silicone rubbers, or LSR's, are elastomers containing 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 petroleum jelly. These materials can be molded into parts and require the use of liquid injection molding equipment.

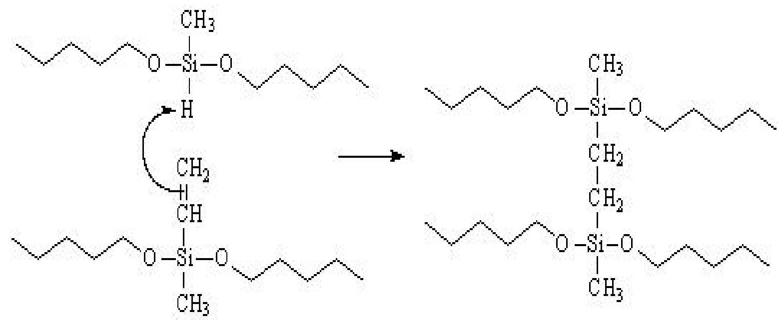
Low consistency silicones are pourable systems composed of lower viscosity polymers and reinforcing fillers such as silica or resin. These systems have lower physical properties than high consistency elastomers or LSR formulations, but can be easily processed and molded by manual methods. These materials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

Adhesives are low consistency elastomers containing 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

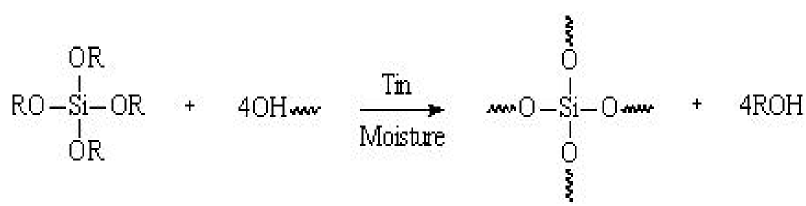
When a manufacturer in the drug delivery industry chooses a material for a specific application, material properties aren't the only deciding factor. That manufacturer also has to examine how the material is used. Inconvenience in production or material by-products can make a chosen material ineffective for a specific application. Silicones, however, can be designed around various cure chemistries to accommodate different production needs. Silicone systems can cure by platinum catalyzed addition cured systems, tin condensation cure systems, peroxide cure systems, or oxime cure systems. Some of the oldest cure chemistry used with silicones utilizes an acetoxy tin condensation cure system. These systems yield a vinegar-like smell (acetic acid), a byproduct of the reaction. This discussion will focus on platinum systems, tin condensation systems, and peroxide systems.

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:



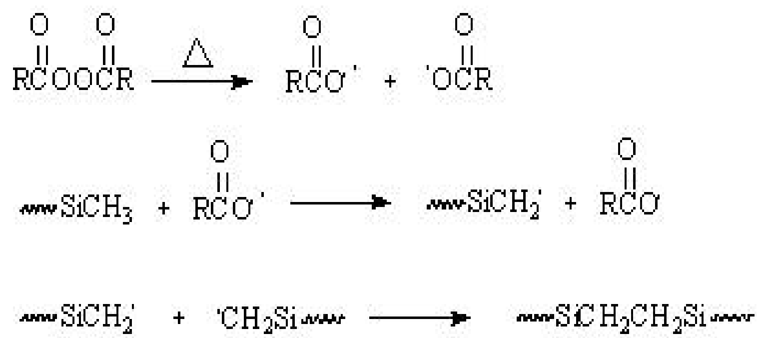
Platinum systems are often cured quickly with heat, but can be formulated to cure at low temperatures or room temperature if necessary. The advantages of these systems include a fast cure and no volatile byproducts. The possibility of inhibiting the cure is the main disadvantage of platinum systems.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

Tin condensation systems invlove 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 condensation systems include the ability to cure at room temperature (useful for temperature sensitive additives) and robust cure systems that are difficult to inhibit. The main disadvantage of condensation systems is the long cure time, as several days are often required to completely cure an elastomer.

Peroxide catalyzed systems, used mostly in high consistency elastomers (see definition below), have a reaction mechanism that involves a peroxide catalyst and either methyl groups or vinyl functional groups. The peroxide catalysts create free radical species of the methyl and vinyl that can then form covalent bonds. Pictured below is the reaction mechanism involving a peroxide catalysis of two methyl groups:



Peroxide systems are typically robust (not easily inhibited) and offer properties such as low tension set (good for balloon applications). Disadvantages include a lengthy post-curing step at high temperatures in order to remove the reaction's byproducts. Other disadvantages include the possibility of the catalyst interacting with active agents.

Discussion

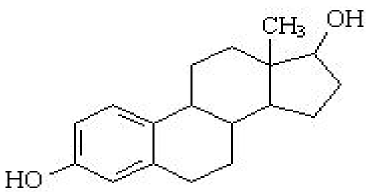
The versatility of silicones as a material enables them to be a viable option for a broad range of drug delivery applications. Some of silicone's specific properties and characteristics, such as its interactive chemistry and microporous structure, make them the material of choice for many drug delivery applications. This can be seen when looking at examples of silicones already being used in healthcare and drug delivery applications.

Interactive Chemistries

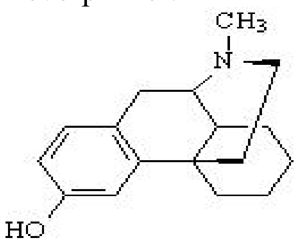
The siloxane polymer backbone of repeating silicon and oxygen atoms creates a potential for interaction. The two free pairs of electrons associated with each oxygen atom can form hydrogen bonds with proton donors. Silicone elastomer systems can be strengthened with silica or resin reinforcement. These systems can result in different degrees of hydrogen bonding.

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 hydrophobicity is ideal for the solubility of pharmaceutical agents having mostly non-polar structures with alcohol or ketone structures. Below are the molecular structures for estradiol, levorphanol, and metrondiazole.

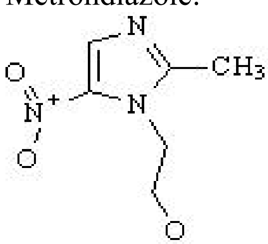
Estradiol:



Levorphanol:



Metrondiazole:



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 a drug delivery device. 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 (3). It can be speculated that the carboxylic acid group competes for siloxane oxygen, thereby reducing the concentration of siloxane oxygen available in the elastomer system. The exact mechanisms and interactions between the silicone polymer backbone and pharmaceutical agents are not known at this point.

Microporous Structure

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 (1). NuSil Technology takes advantage of this phenomenon in the 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.

Healthcare Applications

Silicones expanded into healthcare and medical applications in the 1950's after extensive use in the aerospace industry in the previous decade. Within twenty years, a considerable body of work established that silicone oils and crosslinked siloxane systems did not give rise to harmful consequences when performing subcutaneous, intracutaneous, and intramuscular administrations. In 1954 McDougall reported the cultures of various tissues of warm blooded animals, known to be extraordinarily sensitive to foreign influences, showed no deviation from the usual growth picture on contact with liquid, semisolid, and rubberlike silicone products (10). Silicones have been characterized as biologically and toxologically inert as a result of this work (1). Many applications such as pacemaker leads, hydrocephalus shunts, heart valves, finger joints and intraocular lenses utilize silicone materials.

Drug Delivery Applications

Evaluation and Fabrication

The first step in determining general compatibility of a silicone with an active agent is determining the solubility of the agent in silicone. Silicone oil can be used to determine if an agent may be soluble in a silicone elastomer system (2). Once solubility has been determined, the active agent can then be tested in the elastomer system to determine the optimal concentration or agent configuration for the target release rate per day and the total number of release days. In some devices, the drug is incorporated into a silicone matrix core or reservoir and the release rate is controlled by an outer layer of silicone (without pharmaceutical agents incorporated) on the device. (3,4,5,6,7).

A general review of those patents listed above suggests that 5% to 50% of the active agent is optimal for release rates of 10 to 500 micrograms of drug per day. These numbers are highly dependent on the type of drug, silicone, and any rate enhancing additives. The release rate is also cited on those patents above and has been characterized as essentially zero order.

Commercial Applications

Commercial applications such as Norplant (8) and Femring (9) are examples of clinically successful drug delivery applications that involve silicone materials. Patent number 6,039,968 cites a number of agents that could be used in drug eluting applications. The drugs cited included antidepressants, anxiolytics, vitamins B6, D, and E, antifungal, opioid analgesics, non-opioid analgesics, and antiviral compounds.

Conclusion

As presented above, an investigation of the chemistry of silicone and silicone materials, interactive characteristics, their extensive use in the healthcare industry and current drug delivery applications show the benefits of using silicone materials in a drug delivery device. The paper explored how versatile of a material silicone is and how this can benefit drug delivery. The interaction between drugs, release enhancing agents, and silicone systems was characterized by comparing molecule structures of each. The paper also demonstrated the history of silicone, in various forms, in healthcare applications since the 1950's. Finally, commercially successful examples of products utilizing silicones demonstrate a commitment to silicone as a material of choice for drug delivery applications.

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