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Nusil Silicone Technology in Pharmaceutical Drug Delivery System: A Review

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Subject: Pharmaceutics

Abstract:
This review will investigate the benefits of silicon in pharmaceutical field & as a drug delivery. Nusil silicon technology is a leading formulator and manufacturer of silicone compounds for healthcare, aerospace, electronics and photonics applications. Because of their low toxicity, pure silicones have a low risk of unfavorable biological reactions. Nusil technology offers a complete line of silicone materials for use in the health care industry, in the engineering product, in the packing material as well as in cosmetics. For the drug delivery with any technology it will be needed to study the chemistry of that particular material so the review will also focus on chemistry of silicon, the multiple material composition options and various cure chemistries demonstrating how silicone can be use in specific drug delivery system. The paper will also include brief explanation on silicon interaction with drug which effect silicon 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 and on several applications of Nusil technology in drug delivery system.

Key words: C*osmetics, drug delivery system, healthcare product, Nusil technology, silicone compound*

Introduction:

NUSIL is a world leading formulator of silicone compounds for aerospace, healthcare, electronics and your vital partner in material world, and other applications requiring precise, predictable, cost-effective materials performance. ISO-9001 certified since 1994, NuSil operates state-of-the-art laboratories and processing facilities in North America and Europe and provides on-site, in-person application engineering support worldwide. Today, Nusil Technology comprises hundreds of research, manufacturing and engineering professionals perfecting silicones as materials of choice based on the vast, unique array of properties they provide**.** NuSil Technology has launched the Drug Delivery Silicone (DDS) line of materials and services intended specifically for drug delivery and combination medical device products. For decades, NuSil Technology's line of silicone fluids, elastomers, and gels have been used for drug delivery and medical devices—including matrix and reservoir-type delivery devices for transdermal, transmucousal, and long- and short-term implanted medical devices. Silicones are becoming more popular for their use as adhesives, encapsulate and interface materials due to their thermal stability. Silicones can be customized further by adding various fillers to the polymer that affect the silicone's thermal conductivity, electric conductivity and physical strength. It is important to consider the attributes necessary for each application. A silicone's polymer can be formulated and processed to posses various targeted physical properties. Depending on an application's requirements, properties — such as temperature stability (-115°C to 260°C), fuel resistance, optical clarity (with refractive indexes ranging from 1.38 to 1.57), low shrinkage (2 %), low out gassing and low shear stress — can be optimized to accommodate specific needs. It will also discuss what can distinguish one type of silicone from another based on the chemical composition and reinforcement mode of the silicone polymers.

Silicone Polymer Chemistry:

Silicone is comprised of repeating siloxane units, Si-O, with substituent groups attached to the open valences of the silicon atom. Having no carbon in the backbone, these repeating siloxane units are often referred to as a polysiloxane polymer. Furthermore, silicone polymers are also referred to as polyorganosiloxanes when considering the organic substituent groups.

Silicone Material Types:

Silicone exists in many different forms. By functionalizing the silicone polymer or adding fillers, the composition silicone forms changes. This broad range of material compositions makes silicone a viable option for an endless number of applications. Some silicone material compositions and their typical applications include:

Silicone Fluids:

Silicone fluids are made of non-reactive polymers. The viscosity of the fluid depends chiefly on the degree of polymerization (DP). As the polymer's chain length increases (higher DP), so too does the viscosity. The viscosity range of a silicone fluid is large, ranging from near water (20 cP) to millions of cP. Silicone fluids are used as lubricants, as well as hydraulic or damping fluids in extreme environments.

Silicone Gels:

Silicone gels are made of reactive silicone polymers and reactive silicone cross-linkers in a two-part system. When cured, these gels are designed to have a soft, compliant feel with a range of terminal hardness. Typically, silicone gels are used in situations where low modulus, low stress or self-healing properties are important and posses little to no elastomeric "strength."

Silicone Elastomers:

Silicone elastomers fall into two categories: moldable elastomers and adhesives. Like gels, these two-part systems contain reactive polymers and cross-linkers that cure to form a rubber like elastomer. Elastomers differ from gels however in that they contain reinforcing filler, described in the section below. Most will cure at room temperature; however, some require heat to cure. To impart increased physical properties, these materials will often contain high levels of reinforcing fillers and longer polymer chains that result in higher viscosities. The moldable materials can be cast or injected into molds of various configurations. Elastomers can also be dispersed into solvent systems for use in spraying or dipping applications. Adhesives are low-viscosity elastomers systems that incorporate silicone-based adhesion promoters.

Silicone Resins:

Silicone resins, also known as polysilsesquioxanes, are highly cross linked siloxane systems with the empirical formula:

$$R - Si - O1.5$$

The root "sesqui" indicates the one and a half stoichiometry of the oxygen bond to silicon. These silicones usually have a high modulus and high durometer. By adding resin to silicone polymer, it is possible to increase the hardness of the cured material without increasing the viscosity of the uncured silicon[10].

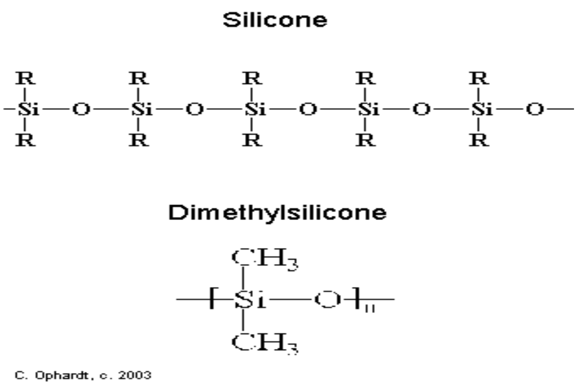
Factors in selecting medical silicone:

Silicone have gained widespread industrial and medical recognition and acceptance, Because of their inherently low toxicity, pure silicones present a low risk of unfavorable biological reactions. The current health-care market supports a small group of manufacturers of silicone raw materials, companies such as General Electric, Wacker, Bayer, Dow Corning, Rhone Poulenc, Shin Etsu, NuSil Technology, and Applied Silicone. Level of testing and commitment to serving particular applications are the primary differences within these suppliers. Historically, concerns over potential financial obligation have driven most large silicone manufacturers to aggressively exclude themselves from providing silicone intended to be used in the human body for more than 29 days. NuSil Technology and Applied Silicone, only two suppliers willing to continue serving the long term implantable.

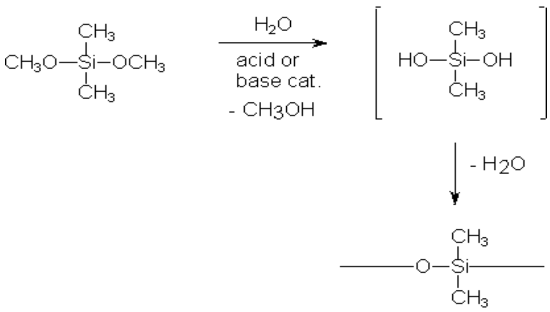
The chemistry behind silicone essentially equates to material versatility, and this versatility allows silicone materials to be custom designed to fit drug delivery applications. An examination of the chemistry of silicone, the multiple material composition options and various cure chemistries demonstrates 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. 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. While concerning the silicones, various designations such as "industrial grade," "health-care grade," "medical grade," and even "implant grade" terms are often use by the device industry. [11]

Polymer chemistry:

The chemistry behind silicone provides the material's versatility and enables it to be custom designed to fit particular drug-delivery applications. The versatile silicone polymer chemistry can provide varying properties useful for different applications. This polymer chemistry, when combined with reactive cross-linkers, catalysts, and reinforcing fillers, leads to a diverse set of material composition. Silicone polymers do not have carbon as part Of the backbone structure. The although silicon is in the same group as carbon in the periodic table, it has quite different chemistry. Many silanes are known which are analogous to the hydrocarbons with Si-Si bonds. These compounds are not very stable and hence not very useful. Silicones have an alternating -Si-O- type structure. This basic structural unit is found in many rocks and minerals in nature including common sand. Various organic groups such as methyl or the benzene ring may be bonded to the silicon as shown in figure below.

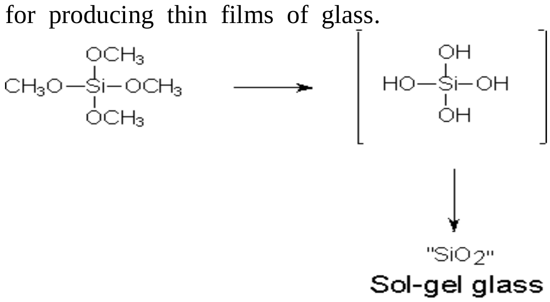


Silicones have a number of medical applications because they are chemically inert. A good deal of controversy has involved the use of silicone in polyurethane bags as breast implants. They were thought to be very inert and resistant to dissolving or other reactions. Reports have cited increased cancer risk and severe immune responses from possible leakage of the silicone from the implants. Some scientist's dispute these findings. Because different constituents can be incorporated onto the polymer, polysiloxanes are used in a wide array of applications. Dimethylsilicones, or dimethylpolysiloxanes, are the most common silicone polymers used industrially. These are typically the most cost-effective to produce and generally yield good physical properties in silicone elastomers and gels. Figure 2 shows the polydimethylsiloxane (PDMS), better known as silicone oil. Note that there are no carbon atoms in the backbone; PDMS has an *inorganic chain.* The glass transition of PDMS is the lowest of all polymers, presumably because of the extremely flexible nature of the Si-O linkage. The linear polymer can also be made by ring-opening polymerization. Cross linked versions of PDMS are important rubbery sealants, caulking's, coatings, and tubing materials. Because of their very low T_g, these materials remain flexible even when extremely cold. The above chemistry can be the basis for crosslinking, so that exposure to atmospheric moisture cures the material. Carboxylate is a common leaving group in silicone bathtub caulking that you can purchase in hardware-stores. As curing proceeds, one can smell acetic acid being liberated from the material.



Polymerization of dimethyl dimethoxy silane.

If the silicone atom is substituted with four leaving groups, the hydrolysis-condensation reaction will eventually lead to materials with the general formula SiO_2. This famous chemistry is known as the sol-gel reaction, and is a method for producing thin films of glass.

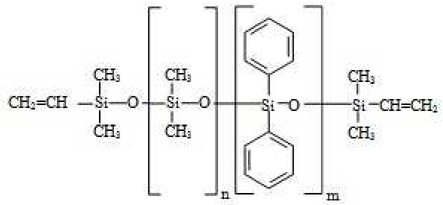


Sol gel glass formation

The reaction mixture(figure has to be heated strongly to drive the product all the way to SiO_2, and lots of by-product (methanol in the above example) is driven off. Therefore, the sol-gel reaction is best performed in thin films which have a lot of surface area to allow evaporation of the by-product. The system shrinks a lot as it cures, making it difficult to produce thick parts with dimensional precision.

Phenyl silicone systems contain diphenyldimethylpolysiloxane copolymers. The steric hindrance of the large phenyl groups significantly prohibits high concentrations of diphenyl units on the polymer chain. The phenyl functionality also boosts the refractive index of the polymers and silicone systems that use these polymers.

Silicone polymers with diphenyl functionality are used to biophotonic applications where higher-refractive-index materials can be used to create a thin lens (e.g., intraocular lenses). Devices with several layers of diphenyl elastomer systems may be created to control release rates of certain drugs. Figure 3 shows a typical structure for a methyl phenyl silicone.



Methyl phenyl silicone

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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 Comfort for the healthcare and drug delivery applications. Some silicone material compositions and their typical applications include:

Silicone Fluids are non-reactive silicone polymers formulated with dimethyl, methyl phenyl, 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 cross linkers. 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.

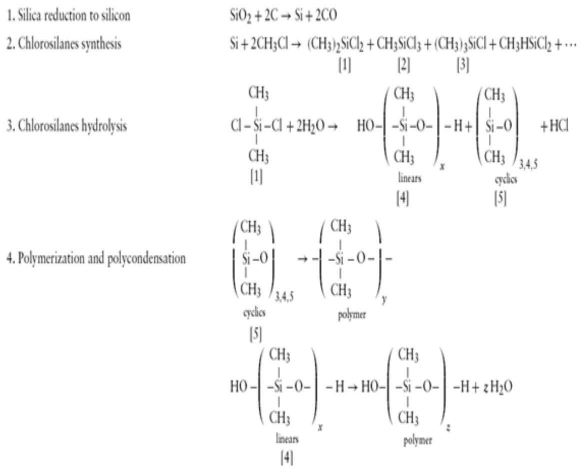
High consistency elastomers typically contain high viscosity polymers and high levels of reinforcing silica. These materials are clay-like in consistency in their uncured state, and offer good physical properties when vulcanized. High consistency materials can be molded into parts by compression or transfer 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 material 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.

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.

METHOD OF PREPRATION OF SILICONE POLYMER:

The advanced synthesis of silicone polymer is miscellaneous and having four basic steps.



Benefits of Silicone:

- Thermal Stability
- Low Ionic Species
- Maintain Optical Clarity (90% minimum @ 400nm)
- Low Moisture Absorption (<0.4%)
- Optimization for UV Resistance
- Adjustable Cure
- Low out gassing
- Low Shrinkage, <1%
- Low Modulus: Stress reduction for bonding materials with different coefficients of thermal expansion.

DIFFERENT TYPES OF MARKETED PREPRATION OF NUSIL:

Nusil used as a drug delivery & cosmetics:

Product name	**Description**	**Application**
DDU-310@1000cPP Silicone Fluid – Drug Delivery Product line	• A clear polydimethylsiloxane liquid Has controlled volatility, lubricating characteristics, and low surface tension • Highly water repellent and resists decomposition by heat and oxidation	• May be considered for use in healthcare applications requiring lubricious and/or hydrophobic coatings • May be considered for applications intended ton facilitate the controlled release of an active pharmaceutical ingredient
DDR-1370 Pressure sensitive silicone adhesive	• One-part, non-curing , • Pressure sensitive Adhesive	• for applications delivering the controlled release of an active pharmaceutical ingredient (API) • May be selected for use in reservoir, matrix and/or drug in adhesive (DIA) transdermal applications

DDR-4355 Silicone gel	• A transparent, tacky silicone gel • A medium viscosity liquid that cures to a soft, high penetration silicone 1:1 Mix Ratio (Part A: Part B)	• May be considered for applications delivering the controlled release of an active pharmaceutical ingredient (API) • May be selected for use in reservoir, matrix and/or drug in adhesive (DIA) transdermal Applications
DDU-4351 Silicone gel	• Pourable, three-component silicone • 97.00 : 2.50 : 0.50 Mix Ratio (Base: Cross linker: Catalyst) • Room temperature vulcanizing (RTV) via condensation cure chemistry	• May be selected for use in healthcare applications requiring a moldable RTV gel • May be considered for applications delivering the controlled release of an active pharmaceutical ingredient (API)
DDU-4630 Silicone elastomer	• Soft, two-part, high tear strength silicone elastomer • Thermally cures via addition cure chemistry • Has a non-tacky surface with no volatile byproducts or peroxide residues • Strained through a 400-mesh screen to ensure freedom from particulate contamination	• May be considered for use in healthcare applications that require the molding or extruding of parts • May be considered for applications delivering controlled release of an active pharmaceutical ingredient (API)
PCM-7918INCI Designation: Amopropyl Bisphenyl Dimethicone Copolymer	• A 50 mol% Bisphenyl Dimethicone copolymer endblocked with aminopropyl groups • PCM-7918 is available at 65,000 cP	• As a formulary component in cosmetics applications

PCM-7949Dimethyl Cyclics	• An octamethyl cyclotetra siloxane	• As a formulary component in cosmetic applications
PCM-7901 And PCM-7802INCI Designation: Dimethicone	• Dimethicone PCM-7901 is available at 350, 1,000, and 12,500 cP	• May be considered for use in Hair Care formulations to add silkiness, shine, lubricity, and detangling • May be considered for use in Skin Care Products to add softness
PCM-7905INCI Designation: Trifluoropropylmethyl Dimethicone	• 100 mol% Trifluoropropylmethyl Dimethicone • PCM-7905 is available at 350, 1,000, and 12,500 cP	• May be considered for use in Hair Care • formulations to add silkiness, lubricity, and detangling
PCM-7907INCI Designation: Trifluoropropylmethyl Dimethicone Copolymer	• A 60 mol% fluoronated copolymer consisting of Trifluoropropylmethyl Dimethicone and Dimethicone • PCM-7907 is available at 350, 1,000, and 12,500 cP	• May be considered for use in Hair Care • formulations to add silkiness, lubricity, • and detangling
PCM-7916 Diphenyldimethicone	• A 30 mole % diphenylsiloxane endblocked with reactive vinyl groups	• As a formulary component in cosmetics applications
PCM-7931 Vinyl Cross polymer and PCM-7932 and PCM-7926		• As a formulary component in cosmetics Application
PCM-7917 Diphenyldimethicone	• A 18 mole % diphenylsiloxane endblocked with reactive vinyl groups	• As a formulary component in cosmetics applications

PCM-7908INCI Designation: Cyclopentasiloxane (and) Dimethicone	• A one-part, low percent solids (15% dimethicone) blend of dimethicone and cyclopentasiloxane • To be used as a formulary component, with minimal mixing required	• For use in Hair Care formulations to add silkiness, shine, lubricity, and detangling • For Skin Care applications requiring an ingredient to add substantivity • May be considered for use as a non-occlusive barrier or film former in personal care systems
Simethicone USP/EP MED-340	• Designated by the FDA-OTC Antacid and antiflatulent • Review Panel as a safe and effective antiflatulent component of antacid and other gastrointestinal preparations	• Provides lubrication for uniform and bubble-free application of topical preparations such as antibiotic ointments and contraceptive gels • Effective in acne and other dermatological ointments, creams and lotions due to its lubricity and anti-whitening properties • As an antifoam in the manufacture and separation of drug products made by microbial fermentation
Simethicone Emulsion USP MED-341	A 30% by weight • emulsion of Simethicone USP • Easy-to-handle emulsion • Highly stable over a broad • pH range • Kosher and Halal certified	• For use in liquid antacids, antiflatulents and as a component of endoscopic diagnostic Aids
Simethicone GS MED-342	• A unique granular solid • Kosher and Halal certified • Easily blends with other tableting ingredients • Eliminates the cost and clean-up of applying liquid Silicone • antiflatulents Contains all Compendial grade components suitable for oral use	• For the manufacture of single- or double-layer tablets • For forming uniform compositions in any concentration required • For effective, stable antiflatulence, even in the presence of aluminum and magnesium hydroxide

PCM-7914INCI Designation: Cyclopentasiloxane Dimethicone Crosspolymer	• A one-part, dimethyl elastomer crosspolymer dispersed in cyclopentasiloxane • To be used as a formulary component, with • minimal mixing required • High viscosity offers the ability to deliver other components easily	• For use in transdermal and cosmeceuticals delivery for vitamins, naturals, and cosmeceutical ingredients • For Skin Care applications requiring an ingredient to impart a silky feeling in creams and lotions • May be considered for use in Scar Management Therapy

Evalution parameter:

Product name	**Evaluation parameter**
Silicon Gel[11]	Viscosity
	FTIR
	penetration(Lab Line Penetrometer, 19.5 g shaft, 1/4th inch foot,5 second)
	Tissue Culture (Cytotoxicity Testing)
	Tensile strength
Silicon Fluid[12]	FT-IR Spectroscopy (Identification)
	Specific Gravity
	Refractive Index
	Collected Volatile Condensable Material (CVCM)
	Total Mass Loss (TML)
	Pyrogenicity
	Systemic Toxicity
	Intracutaneous Toxicity
Silicon Adhesive	Viscosity
	Non-Volatile Content
	FTIR Spectroscopy
	Release Force of PSA
	PSA Blunt Probe Test
	Tissue Culture (Cytotoxicity Testing)
Cosmetics	Physical state
	Refractive index
	Total mass loss
	Acid number
	Flash point
	Specific gravity

APPLICATION:

1) As health care:

Healthcare Applications NuSil Technology's healthcare materials are classified as unrestricted or restricted. Unrestricted products may be considered as candidate materials for any application, including long term implantation of greater than 29 days. Usage of Nusil's restricted products, however, is limited to external use or for short term implant application of 29 days or less[13]. In 1993 NuSil Technology was uniquely positioned to respond to the availability crisis of silicone materials for use in long term implant applications in the medical device market. Well established in the medical silicone market and having firsthand knowledge of the products that were being discontinued, NuSil Technology responded to this situation by providing over 25 replacement products that are clones of discontinued originals manufactured by other companies. Using this expertise, **NuSil Technology** expanded this line of high performance silicones to offer competitively priced materials for use in external applications or for medical devices implanted up to 29 days in the body. Many of these silicone biomaterials are used in applications requiring USP Class VI certifications. Full testing and traceability are offered on these products as well. Silicone expanded into healthcare and medical applications in the 1950's after extensive use in the aerospace industry in previous decade. Within twenty years, silicone oils and cross linked siloxane system did not give rise to harmful consequences. When performing subcutaneous, intracutaneous, and intramuscular administrations. Many applications such as pacemaker leads, hydrocephalus shunts, heart valves, finger[14] joints and intraocular lenses utilize silicone material.

2) Drug Delivery Application:

The first step in determining general compatibility of a silicone with an active agent is determining the agent's solubility in silicone. Silicone oil can be used to determine whether an agent may be soluble in a silicone elastomer system. Once solubility has been determined, the active agent can then be tested in the elastomer system to establish 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 outer layer of silicone (without pharmaceutical agents incorporated) controls the release on the device. Such information can be found on patent registration forms. A general review suggests that 5–50% of the active agent is optimal for release rates of 10 to 500 µm of drug per day. These numbers are highly dependent on the type of drug and silicone, as well as any rate-enhancing additives. The release rate is also cited on patents and has been characterized as essentially zero order.[15,16]

3) Cosmetic Application:

Today announced the launch of specialized silicone formulation services to the cosmetic industry. Cosmetic companies will be able to obtain custom fluorosilicone and phenyl silicone polymers and film formers. "NuSil Technology has essentially opened its research and development laboratories to the cosmetic industry" stated Brian Nash, Vice President of Marketing and Sales.[17]

4) Commercial Applications:

Commercial applications such as Norplant and Femring 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.[18]

5) Fluorosilicones in the Aerospace Industry:

Fluorosilicone's advent into the commercial marketplace offers opportunities for manufacturers to pursue new applications for silicones in the automotive, aircraft and general markets. The unique properties of fluorosilicones provide a solution for products that need broad operating temperatures, fuel resistance and long-term reliability[16,18].

6) **Choosing a Silicone Encapsulant for Photovoltaic Applications**:

Non-phenyl containing 1.41 RI silicones have been used for several years for bonding solar arrays in the satellite industry. Phenyl groups on the siloxane polymer can change various properties of silicone.

7) Understanding the Role of Silicones in Controlled Release Applications:

Silicones possess certain dynamic characteristics which allow them to be compounded in with a host of actives. These same unique characteristics also allow them to release those actives from a molded/extruded device in a predictable way – whether that application is for transdermal, transmucosal, short or long-term human implantation.

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17. http://www.nusil.com/mediarelations/2004/press-release8.aspx
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