Silicones in Pharmaceutical Applications.  
Part 5: Siliconization of  
Parenteral Packaging Components

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Abstract
Most parenteral packaging components (e.g., needles, syringes, stoppers, vials, etc.) require the use of some form of surface treatment or lubrication in order to improve their processability and functionality. This article will review the materials used for and the process of siliconization as well as subsequent sterilization of siliconized articles and clean-up of silicone fluids.

1. Introduction
Polydimethylsiloxane (PDMS), otherwise referred to as silicone fluid, is currently the most common surface treatment used for parenteral packaging components. The application of PDMS to the interior walls of glass vials in order to facilitate drainage and promote product homogeneity by reducing the glass surface energy and preventing the pharmaceutical solution from wetting out the container surface was first patented in 1950. “Siliconization” and/or deposition of a thin film of silicone fluid onto glass vials and rubber stoppers/closures is probably one of the oldest applications for silicone in the pharmaceutical field. Based on historical literature citations for siliconization of parenteral packaging components, thin silicone coatings were shown to be useful in providing: clean and complete drainage from multiple dose vials, lubricity to glass cartridges in disposable syringes, machineability to rubber cap components and defoaming or de-aeration action of reconstitution powders, when necessary. In addition, thin films of silicones received regulatory approval for use as lubricants for hypodermic needles.

2. Siliconization
Surface treatment with silicone fluid (siliconization) is carried out by applying low concentrations (via spraying, wiping or dipping) of either a solvent or emulsion based liquid containing silicone fluid to a clean, dry surface. The film is then either air dried or “baked” at an elevated temperature to improve film adhesion on the surface. Silicone in the preparation of parenteral packaging components should meet appropriate quality control criteria and not have any adverse effect on the safety, quality, or purity of the drug product.

Although quantification of film thickness/concentration is difficult due to the very low levels of fluid required to wet-out the surface, some analytical techniques have been successfully used, such as Atomic Absorption. More frequently, however, users rely on functional tests (e.g. contact angle or coefficient of friction measurements) to determine the efficacy or effectiveness of the coating. For certain applications, such as needle coatings, specific testing equipment has also been designed. For instance, Melab GmbH has developed equipment that can be used to measure the various penetration stages of a cannula tip as it pierces and penetrates a foil.

Currently, there are three different types of silicone products available for use as a packaging lubrication aid: non-reactive silicone fluid, nonreactive silicone emulsion, curable silicone fluid.

2.1 Non-reactive Silicone Fluids
Dimethicone fluids (e.g., Dow Corning 360 Medical Fluids and Dow Corning Q7-9120 Fluids) are clear, colorless materials which are available in several standard viscosities. Chemically, the fluids are linear polymer (polydimethylsiloxane) which contains the repeating polymer units of the formula:

\[
\begin{align*}
\text{CH}_3 & \quad \text{Si} \quad \text{O} \quad \text{Si} \quad \text{O} \quad \text{Si} \quad \text{O} \\
\text{SiMe} & \quad \text{CH}_3 \\
\end{align*}
\]

The linear unit is “terminated” with trimethylsiloxy units. The structure of dimethicone fluid can be represented as an \( \text{Q}, \text{Q}-\text{bis}-\text{trimethylsiloxy} \text{polydimethylsiloxane} \) and is ideally represented by the following structural formula:

\[
\begin{align*}
\text{H}_3\text{C} \quad \text{Si} \quad \text{O} \quad \text{Si} \quad \text{O} \quad \text{Si} \quad \text{O} \\
\text{SiMe} & \quad \text{CH}_3 \\
\end{align*}
\]

The viscosity of the final fluid is directly related to the chain length, i.e., to the average value of “x” in the above formula and is controlled by

<table>
<thead>
<tr>
<th>PDMS Fluid Viscosity, cSt</th>
<th>Molecular Weight (No. average) ( M_n )</th>
<th>( \text{Me}_2\text{SiO(Me}_2\text{SiO})_x \text{SiMe}_3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1,960</td>
<td>26</td>
</tr>
<tr>
<td>100</td>
<td>5,800</td>
<td>78</td>
</tr>
<tr>
<td>350</td>
<td>9,500</td>
<td>128</td>
</tr>
<tr>
<td>1,000</td>
<td>17,300</td>
<td>234</td>
</tr>
<tr>
<td>12,500</td>
<td>37,300</td>
<td>504</td>
</tr>
</tbody>
</table>
the ratio of trimethylsiloxy units to dimethylsiloxy units in the product during processing/manufacture. The average molecular weight can be measured for any polydimethylsiloxane (PDMS) fluid by performing Gel Permeation Chromatography (GPC). The number average molecular weight for the different fluid viscosities are shown in Table 1.

Dow Corning first commercialized polydimethylsiloxane in 1945. Since 1945, the production facilities and processes have been expanded and undergone continuous improvement to meet the demanding market needs; however, the basic process (chemistry) and structure (composition) have remained unchanged over that period of time.

Some trimethylsiloxy-endblocked polydimethylsiloxane fluids are produced, tested, packaged and certified to meet the non-parenteral Dimethicone NF monograph. Dimeticonum Ph. Eur. or Silicone Oil used as a Lubricant Ph. Eur., depending on the fluid viscosity. Fluids depyrogenated prior to packaging are often used as a packaging component for parenteral products. These trimethylsiloxy endblocked polydimethylsiloxane fluid polymer and commonly referred to as PDMS, Dimethicone or Dimeticone.

A common method for applying trimethylsiloxy-endblocked polydimethylsiloxane fluids involves spraying the pure fluid; however, some types of articles are dipped in fluid to treat them while others may be wipe-treated via a sponge or other wiping material. Regardless of the application method, it is critical to only apply enough fluid to achieve the desired lubrication as excess fluid could come off as particulates/impurities.

Baking removes any moisture of hydration on the surface and allows the silicone fluid to become more intimately associated with the surface. In addition, at elevated temperatures the silicone fluid is prone to some oxidation and crosslinking, which further enhances its durability on the coated substrate.

The first monolayer of silicone fluid applied to a surface is more durable due to a physical attraction to the surface. The heat also allows small droplets of silicone fluid to spread out over the substrate and create a more uniformly treated surface. If an article is baked, it is suggested that the temperature be maintained below 250°C (to minimize formaldehyde formation) for less than 2 hours. Higher temperatures have been used at substantially shorter time periods.

Some increase in durability or decrease in mobility may also be achieved by using a higher viscosity fluid. Higher viscosity fluids should not flow as easily across a surface and tend to come off as particulates as easily.

Below 150°C, trimethylsiloxy-endblocked polydimethylsiloxane fluids are typically chemically inert and resistant to decomposition; however, higher temperatures or the presence of certain metals can have an impact on their reactivity and decomposition. In addition, polydimethyl siloxane fluids have low surface tensions, are water repellent (hydrophobic) and act as good lubricants for glass, rubber and plastics. Very thin films of PDMS are applied to the barrels of glass and plastic syringes to ensure smooth operation of the plunger as well as provide a hydrophobic surface to minimize wet-out of the drug. Likewise, this fluid can be applied to hypodermic needles to allow easier penetration through the skin.

Toxicology studies have shown these materials to have a low order of toxicity.

2.2 Non-reactive Silicone Emulsion

A water-dilutable, non-reactive PDMS fluid emulsion containing nonionic emulsifiers and about 35% National Formulary Dimethicone fluid has also been used for a variety of applications where it is advantageous to deliver a lubricating silicone fluid in a water-dilutable delivery system. At room temperature, Dimethicone NF Emulsions are normally visually clean, white, low viscosity liquid which are completely miscible in water; however, separation/settling can occur; therefore, containers should be thoroughly mixed prior to and if necessary, during use.

The most widely used method of application is spraying a diluted emulsion. Some types of articles may be dipped in a diluted solution of the emulsion while others may be wipe-treated via a sponge or other suitable wiping material.

Whatever the method of treatment, it is important to consider how much fluid from the emulsion is being applied to the article since excess fluid (beyond that needed to achieve lubrication) may come off the article and become an impurity in solutions such as drugs delivered in siliconized syringes.

As with the non-reactive silicone fluid, films produced from the silicone emulsions can be made more durable by “baking” the article after treatment.

2.3 Reactive Silicone Dispersion

An amino functional silicone polymer dispersed in a 50% co-solvent consisting of 85% aliphatic hydrocarbon solvent and 15% isopropanol (IPA) has also been shown to be effective at siliconizing parenteral packaging components.
The amino-functional polymer contains a small number of reactive groups at the ends of the polymer chain that can crosslink or “cure” on the surface being treated. The curing process requires the presence of moisture to achieve optimum properties. The curing process is chemically described by the following reaction:

In the presence of moisture, the methoxy groups (-OCH3) are hydrolyzed to form hydroxyl groups (-OH). The hydroxyl groups are extremely reactive and react with other functional groups present on a substrate or with other hydroxyl groups present on the silicone polymer (to form a higher MW polymer). The condensation reaction is catalyzed by amine groups that are present on the silicone polymer. Thus, the silicone polymer can attach/cure to most reactive surfaces and by intra-molecular condensation and the amino groups are not removed during curing, but rather, they are crosslinked into the polymer network.

This dispersion provides:
- A room-temperature curable coating
- A chemical functionality that attracts the coating to polar surfaces (metals and some plastics)
- More substantive coating than pure polydimethylsiloxane fluid
- Coating that is widely accepted for lubricating hypodermic needles

3. Sterilization
The silicones stability and their low reactivity allow for them to be sterilized by steam autoclaving, dry heat, ethylene oxide and low doses of radiation.

Ethylene oxide (100%) has been shown effective for the sterilization of disposable hypodermic needles and syringes. If ETO is used, proper out-gassing is required before the article is suitable for use.

Steam autoclaving or dry heat sterilization have also been shown to be acceptable sterilization technique.

It has been found that radiation sterilization generally has no effect on the fluid if doses up to 2.5 Mrad are used; however, it is recommended that articles that are radiation sterilized should be tested for proper lubrication before and after the sterilization process. Although the effects of radiation sterilization are not completely known, it is well understood that at high levels of radiation (> 2.5 Mrad) there is a tendency for radiation to cause crosslinking in PDMS, which may cause coatings to harden, thus impacting their ability to lubricate.

4. Cleaning
To remove PDMS fluids from a surface that was inadvertently treated, the most effective cleaning agents are aliphatic and aromatic solvents; however, these materials may not be permissible for use in clean room areas since they are flammable. If a water-based detergent is desirable for cleaning and for use in clean-room areas, clean-in-place (CIP) detergents (e.g. potassium hydroxide or phosphoric acid based) have been found useful and effective. These detergents are currently widely used in pharmaceutical plants to clean PDMS from equipment.

5. Conclusions
Rubber parts, such as vial stoppers, syringe plungers, tip caps and needle guards are the most frequently lubricated components used in pharmaceutical manufacture. Lubrication is often achieved by direct application of the PDMS fluid to the parts via calibrated sprayers or atomizers. These components can also be lubricated using emulsions or dispersions. This is often accomplished via rinsing and/or direct immersion of parts.

PDMS fluid is often applied to syringe barrels, glass vials and other glass parts by coating with emulsions or solutions. Following application, to increase durability of the fluid, it can be “baked” on to the glass parts by means of dry heat.

Since a potential source of contamination for parenteral products is the siliconization of rubber components, silicone used in the lubrication/treatment of parenteral packaging components should meet appropriate quality control criteria and not have an adverse effect on the safety, quality, or purity of the drug product.

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11. Dow Corning Data Sheet for Dow Corning® MDX4-4159.