Next Generation Lubricant Technology for Parenteral Syringes and Cartridges

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Overview

- Problems with Silicone Oil
  - Drug Stability
  - Syringe/Device Performance
- Comparison of Silicone Oil and SiO₂ Lubricant
- How the SiO₂ Lubricant is Applied
  - Balancing Performance Attributes
- Plunger Force Performance
- Particulate Performance
- Extractables – Toxicology Assessment
"We found that the presence of silicone oil microdroplets in OVA formulations caused structural perturbations in the protein which were detected after only relatively short periods of exposure to silicone oil-water interfaces."


"[Silicone oil] maybe responsible for the phenomenon of soluble-protein loss... and the irreversible adsorption of protein may be associated with protein denaturation/aggregation."


“The most probable explanation for silicone oil induced aggregation is that the oil has direct effects on intermolecular interactions responsible for protein association through interaction with protein surfaces or indirectly through the effects of the solvent.”


“Silicone oil-coated syringe components provide a chemical and structural environment on which proteins can denature and aggregate.”

- Immunogenicity Assessment for Therapeutic Protein Products; US Dept.of Health and Human Services; FDA, CDER, CBER; Aug 2014.
## Contrasting Silicone Oil & New Lubricant

<table>
<thead>
<tr>
<th></th>
<th>Silicone Oil</th>
<th>New Lubricant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Application to Syringe Barrel</strong></td>
<td>Spray a solvent or emulsion based solution with polydimethylsiloxane</td>
<td>Plasma Enhanced Chemical Vapor Deposition (PECVD)</td>
</tr>
<tr>
<td><strong>Plunger Force Control</strong></td>
<td>Increase molecular weight &amp; cross-link</td>
<td>PECVD process parameters (cross-link)</td>
</tr>
<tr>
<td><strong>Subvisible Particles (&lt;15µm) (Particle Count/ml)</strong></td>
<td>Range (30,000 – 50,000)</td>
<td>Range (500 - 1,000)</td>
</tr>
<tr>
<td><strong>Coating Distribution After Aging</strong></td>
<td>Migrates over time</td>
<td>Stationary until plunger moves moves</td>
</tr>
<tr>
<td><strong>Molecular Structure</strong></td>
<td>Linear chain polymer - Polydimethylsiloxane</td>
<td>Amorphous, crosslinked polymer</td>
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</table>

**Molecular Structure Diagrams**

- **Silicone Oil**: Polydimethylsiloxane (linear chain polymer)
- **New Lubricant**: Amorphous, crosslinked polymer
- Measured by optical reflectance spectroscopy
  - Non-destructive
  - Fast (1-2 seconds/measurement)
  - Adaptable for vials, syringes, and cartridges

- Average lubricant coating thickness was 460 nm and its volume estimated at 0.15 µL
  - This is less than half the volume of silicone oil on 1mL glass syringes (approximately 0.5 µL)

- Thickness distribution and volume of lubricant can be tailored to virtually any syringe or cartridge size by the PECVD process
New Lubricant Deposition Process - PECVD

Plasma Enhanced Chemical Vapor Deposition (PECVD)

Octamethylcyclotetrasiloxane

Plasma

\[ \text{H}_3\text{C-Si-Si-Si-C}_3\text{H}_3 + \text{O}_2 + \text{Ar} \rightarrow \text{CO}_2 + \text{H}_2\text{O} + \text{Ar} \]
Controlling Lubricant Cross-link Density

Plasma Energy Density = \( \frac{\text{Applied Energy}}{\text{Mass of Gas Mixture}} \)

Lubricant Coating

Chemically Resistant Protective Coating

Barrier Coating

Cross Link Density

How do you characterize and tailor this & why?

Plasma Energy Density (KJ/kg)

Low

Intermediate

High
Why Tailor Cross-link Density?

Balance Plunger Force & Particle Loads
How to Characterize Cross-link Density? – FTIR Spectroscopy

Monomer for New Lubricant – A Chemical Fingerprint

Octamethylcyclotetrasiloxane

- Liquid @ RT
- MW: 296.61g/mol
- T_{bpt}: 175-176° C
- Viscosity: 2.5cSt
- P_{vapor}: 100Torr

Absorbance

Wavenumber (cm\(^{-1}\))
Effect of Lubricant Cross-linking on FTIR Spectra

(High Cross-Link Density) $A < B$ (Low Cross-Link Density)
Plunger Force - Effect of Cross-linking

Constant Applied Force @ 300mm/min

Silicone Oil on Glass

<table>
<thead>
<tr>
<th>Force (N)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
</tr>
</thead>
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<td>Displacement (mm)</td>
<td>0</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td></td>
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Initiation Force (Fi): 9±2N
Maintenance (Fm): 3±1N

New Lubricant on Coated COP

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<tr>
<th>Force (N)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
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Initiation Force (Fi): 10±2N
Maintenance (Fm): 4±1N

After 7 days stored @ RT

After 2 years
Particulates – Effect of Cross-linking

(Particle Diameter Range: 2-50µm)

- Filled w/ Citrate Buffer Solution
- 10min shake @ 1000rpm
- Solution expressed through needle into MFI injection port

*Particle analysis by microflow digital imaging which detects particles between 2 - 100 µm.
Analytical Experiments:
- Solvents: H$_2$O, H$_2$O (pH 4), H$_2$O (pH 8), IPA
- Spiked solvents: 4 different siloxane compounds
- Procedure: whole article, boiled under reflux for 24 hours. Five (5) syringes in 200 mL, 50-mL aliquot concentrated to 1ml
- Semi-volatile compounds: (GC-MS w/ EI)
- Non-volatile polar compounds: (HPLC-UV-MS w/ APCI)
- Volatile impurities & residual solvents: (HS GC-MS)

Extraction Test Setup
Extractables Testing

- Aqueous extractions:
  - No compounds exceeding AET (0.75µg/syringe)
  - No peaks were attributable to extracted siloxane compounds

- IPA extractions (rigorous):
  - Peaks associated with siloxane compounds were found in extracts
  - Specific siloxane compound identification was not conducted because each compound was below the AET (0.75µg/syringe)

- Spiked extract identification:
  - None of the four spiked siloxanes were recovered from aqueous extracts
  - All four siloxanes were recovered from IPA extracts
Toxicology Assessment of New Lubricant

- Report Title: Literature-Based Toxicological Assessment of Siloxane Leachable Targets
- Prepared by: SciScout LLC

Summary: Siloxane leachable targets extracted from the device, at the maximum possible exposure concentrations, do not pose a concern for human health risk, from pediatric through geriatric populations for local or systemic exposures to the leachable targets that may occur during the suggested clinical use of the device.

- No siloxane compounds exceeding maximum exposure concentrations
Summary

- Silicon-based lubricant
- Solid lubricant applied uniformly on syringe barrel by PECVD process
- Process highly reproducible
- Lubricant balances consistent plunger forces and low subvisible particulates
- Low extractables
- Safe (Toxicology Assessment)
Thank you for your time.

SiO$_2$ Medical Products, Inc.
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