

## Brief/Technical Note

# Effect of Processing Parameters on the Physical Stability of Silicone Coatings

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## INTRODUCTION

Prefilled syringes have emerged as a container of choice for the storage and delivery of protein pharmaceuticals. This is due to a number of factors including greater medication safety resulting from reduced dosage errors, ease of use, and significantly reduced overfill requirements (1,2). Proper functionality of the prefilled syringes is achieved by lubricating the syringe barrel and plunger tip. For the past several decades, silicone oil has been the material of choice for this purpose. Recently, silicone oil has been implicated in causing enhanced protein aggregation in formulations delivered through prefilled syringes (3–5).

The process of protein aggregation in formulations stored in prefilled syringes can, in general, be ascribed to the following steps: protein adsorption to the hydrophobic silicone oil/water interface, surface-induced protein denaturation, desorption of the denatured species, and aggregate formation following association with similar molecules in the bulk. Since protein binding to the silicone oil constitutes the earliest step in this aggregation process, it is critical to inhibit/reduce this binding.

In prefilled syringes, silicone oil is available in two forms with which a protein can interact: surface bound and free. Surface-bound silicone oil provides a static interface with water in a device. Free silicone oil is present because of the application of excess silicone oil or a poor coating process, which may leach into the bulk. The leached silicone oil poses an additional concern as it provides an increased interfacial area for protein adsorption. Moreover, from a regulatory perspective, the enhanced particulate load because of silicone oil leaching can be a problem (6). Since the only purpose of silicone oil in prefilled syringes is to provide lubricity for a smooth plunger movement, it is important to optimize the

amount of silicone oil that is applied to the surface to maintain an optimum syringe gliding force without generating any excess silicone oil on the surface. Excluding this excess silicone oil, which is prone to leaching, will result in a reduction in the silicone oil/water interfacial area with which a protein can interact, making the protein binding to the silicone oil a rate-limiting step in the process of silicone oil-induced protein aggregation. As more and more biologics are becoming available in prefilled syringes, it is critical to reassess the process of silicone oil coating in syringes. In a recent study, silicone migration from cyclic olefin copolymer syringes, coated with silicone, was studied as a function of curing process and formulation parameters (7); however, most of the work done by the industries in this area is proprietary and is seldom published.

From a point of gaining a mechanistic understanding about the effect of different parameters on the stability of silicone coating at a surface against leaching, we evaluated the physical stability of silicone films in distilled water as a function of curing temperature, the applied amount, and viscosity of silicone fluid.

## MATERIAL AND METHODS

Silicone oil (poly(dimethyl siloxane), trimethylsiloxy terminated; PDMS) of varying viscosities, viz. 100 and 350 cSt (Medical Fluid® 360 Dow Corning Inc.), 1,000, 10,000, and 1 millioncSt (UCT Specialties LLC) were obtained. Analytical-grade hexane was obtained from Fisher Scientific (New Jersey). Deionized water equivalent to Milli-Q™ grade, further filtered through 0.1- $\mu$ m PVDF filters (Millipore, Billerica, Massachusetts), was used.

### Silicone Oil Coating

AT-cut quartz crystals with optically flat polished gold/titanium electrodes with a fundamental resonant frequency of 5 MHz and active electrode area of  $\sim 0.4$  cm<sup>2</sup> were obtained from Stanford Research Systems (SRS, Inc., Sunnyvale, California). Crystals were first cleaned with piranha solution (one part of 30% hydrogen peroxide in three parts of 95–98%

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sulfuric acid) and then rinsed thoroughly with deionized water and ethanol, followed by drying with high-purity nitrogen. The resonant frequency of the blank crystal was recorded. Solutions of PDMS were prepared in hexane with desired polymer concentrations. The polymer solutions were then casted on 5 MHz gold-plated quartz crystals using the method reported earlier (8). The films were then dried for 2 h at different temperatures as desired, viz. room temperature ( $\sim 22^\circ\text{C}$ ),  $100^\circ\text{C}$ , and  $150^\circ\text{C}$ . After drying, the resonant frequency of the polymer-coated crystal was measured. The difference between the resonant frequencies of the uncoated and coated crystals was determined. The shift in the crystal resonant frequency is directly related to the mass of the deposited polymer on the surface using the Sauerbrey equation (Eq. 1) (9).

$$\Delta F = -\frac{2F_o^2}{A\sqrt{\rho\mu}}\Delta m \quad (1)$$

where  $\Delta F$  is the frequency shift (in hertz),  $F_o$  is the resonant frequency of the crystal (in hertz),  $\Delta m$  is the adsorbed amount (in grams),  $A$  is the active electrode area (in square centimeters),  $\rho$  is the density of quartz ( $2.648\text{ g/cm}^3$ ), and  $\mu$  is the shear modulus of quartz ( $2.947 \times 10^{11}\text{ g/cm}^2\text{s}^2$ ). According to the equation, a negative 1 Hz shift in the frequency corresponds to a mass deposition of  $\sim 17.7\text{ ng/cm}^2$ .

### Testing the Physical Stability of Silicone Oil Coatings

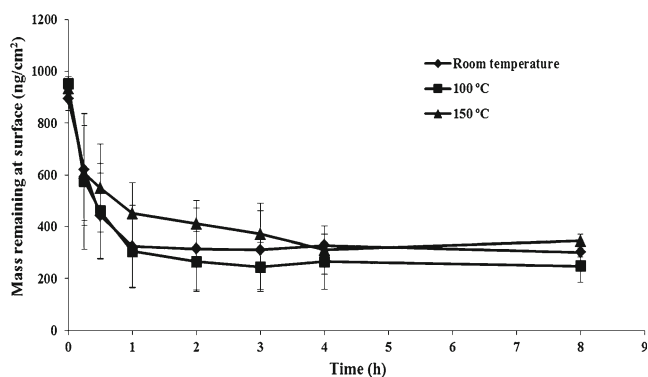
In order to test the stability of the PDMS film in an aqueous environment, the coating was exposed to deionized water for different time periods (ranging from 15 min to 8 h) in static mode as follows: sufficient volume of water ( $\sim 200\ \mu\text{L}$ ) was carefully placed on the PDMS coating casted on the crystal surface, avoiding any significant disturbances to the coating. After each given time interval, water was gently lifted from the surface using a micropipette; crystals were then dried using high-purity nitrogen. The resonant frequency of the dried crystal was measured to determine the net frequency change due to water exposure. All the measurements were made at room temperature ( $\sim 22^\circ\text{C}$ ).

## RESULTS AND DISCUSSION

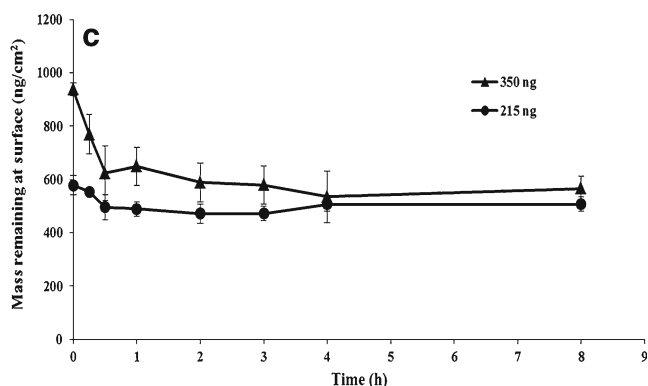
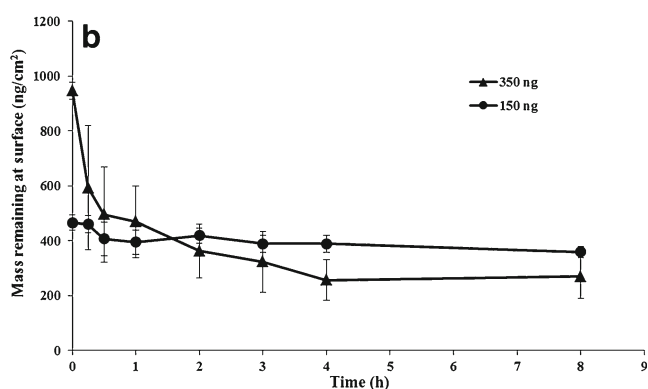
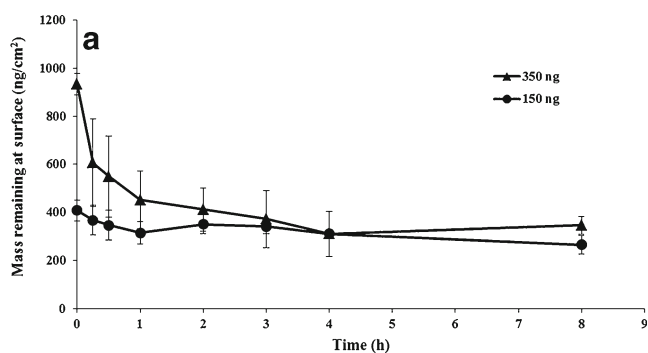
Quartz crystal microbalance (QCM) provides a sensitive method (in nanograms per square centimeter) to measure the adsorption/desorption of a species at an interface (10). This technique was used to monitor the amount of coated silicone (PDMS). PDMS coatings were exposed to triple-distilled water. The amount of PDMS used to coat a crystal was calculated based on the area of dimethylsiloxane monomer (11) and the active crystal area. Approximately 350 ng of the PDMS (average  $\Delta F \sim -50\text{ Hz}$ ), sufficient to give a few monolayer thick and elastic coating on the crystal surface, was deposited. The amount deposited was further modified, if needed, as discussed further.

### Effect of Curing Temperature and Deposited Amount on Coating Stability

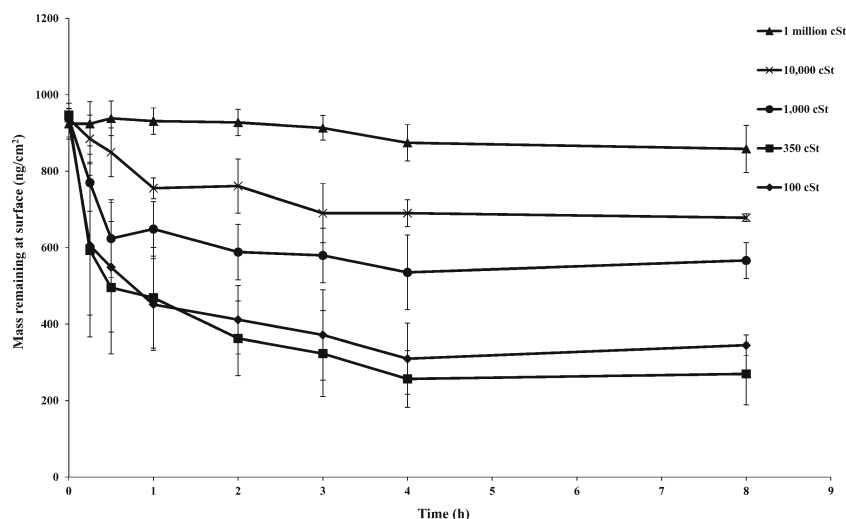
The physical stability of films in distilled water, casted using 100 cSt-grade PDMS, as a function of curing



**Fig. 1.** Comparative physical stability of 100 cSt PDMS, cured at different temperatures, in distilled water as a function of time. The mass has been calculated from the Sauerbrey equation using the frequency shifts measured with QCM



**Fig. 2.** Comparative physical stability of **a** 100, **b** 350, and **c** 1,000 cSt viscosity grades of PDMS, cured at  $150^\circ\text{C}$ , in distilled water as a function of time for different amounts of deposited polymer. The mass has been calculated from the Sauerbrey equation using the frequency shifts measured with QCM



**Fig. 3.** Comparative physical stability of different viscosity grades of PDMS films, cured at 150°C (except 1 millioncSt PDMS, which was cured at 100°C), in distilled water as a function of time. The mass has been calculated from the Sauerbrey equation using the frequency shifts measured with QCM

temperature is shown in Fig. 1. Three observations can be made from the graph; first, PDMS comes off the surface as the exposure time of the coatings to water increases until a stable level is reached in  $\sim 2$  h. Second, there are large errors ( $>20\%$ ) associated with the mass changes upon exposure to water. Third, curing temperature, within error, does not seem to affect the stability of the PDMS coating towards water exposure. The loss of the deposited polymer from the surface in water could be attributed to its solubility in water. However, it has been reported that there is an inverse and exponential relationship between the PDMS solubility and its molecular weight (12). A linear PDMS with  $n=3$  ( $n$  being the number of dimethylsiloxane monomer units in PDMS) and molecular weight 310 has been reported to have a solubility of  $\sim 70$  ppt (12). This suggests that the PDMS grades used here should have essentially no measurable water solubility (where  $n$  is 72 (100 cSt) and 132 (350 cSt); for other grades,  $n$  is unknown due to the unavailability of number average molecular weight but should be significantly larger because of higher viscosity). In such a case, the possibility for the polymer loss could be attributed to the physical leaching of the loosely bound top polymer layers. The physical leaching of silicone oil can occur because of the mechanical shock encountered by a lubricated device during different processes such as product filling, shipping, or freeze-thaw (4,13). Although utmost care was taken while exposing the coatings to water, the fluid drag was sufficient to remove the coating partially and points towards the potential of silicone leaching when a coated device encounters a significantly larger magnitude of physical drag during the real pharmaceutical settings. Moreover, if solubility would have been in play, each successive exposure would have removed additional deposited polymer from the surface, and the mass of the polymer remaining at the end of the studies should have been close to zero (all PDMS desorption). Since this was not observed, the leaching could only be attributed to excessive PDMS on the surface. To confirm if this indeed is the case, a PDMS amount equal to that remaining at the surface at the end of 8 h,  $\sim 150$  ng, in Fig. 1 was deposited, and the films

were cured at 150°C. This mass corresponds to  $\sim 13$ -monolayer-thick coating, assuming a stacking arrangement of the dimethylsiloxane chains on the crystal surface. The results in Fig. 2a show that deposition of an optimum amount of the polymer reduced the leaching significantly and also led to a reduction in the error that was associated with each successive water exposure. Similar results were also seen with higher viscosity polymers viz., 350 cSt ( $\sim 150$  ng) and 1,000 cSt ( $\sim 215$  ng), where leaching and large errors in mass changes were observed with larger deposited amounts, but were reduced significantly upon depositing an optimized amount as shown in Fig. 2b and c, respectively. The higher temperature can remove the water of hydration (14). This results in an intimate association of the polymer with the surface. Therefore, 150°C was used to cure the polymer coatings in Fig. 2b and c. Temperatures above 150°C were avoided as PDMS has been reported to undergo thermal degradation in air at higher temperatures (15,16).

#### Effect of Polymer Viscosity on the Coating Stability

Figure 3 shows the effect of PDMS viscosity on the physical stability of coatings in the presence of distilled water. The results are compared for equal amounts ( $\sim 350$  ng) of deposited PDMS, with coatings cured at 150°C, except for 1 million cSt, which was cured at 100°C. All polymer grades, other than 1 millioncSt, showed an initial polymer desorption (during the early  $\sim 1$ – $2$  h), followed by a leveling of mass remaining at the surface. This initial desorption was a function of polymer viscosity. The change in the initial slope was higher for the lower viscosity grades. The 1 millioncSt viscosity PDMS did not lose any deposited material. A clear trend, qualitatively, was seen between the polymer viscosity and its tendency to stay at the surface in the presence of water (the higher the viscosity, the higher the stability against desorption). A higher viscosity fluid is not expected to flow easily and hence comes off the surface because of its decreased mobility (increased durability).

## CONCLUSION

A significant reduction in the bulk leaching of lower viscosity grades of silicone (PDMS) was observed when the coatings were casted using an optimum polymer amount. The stability of the films against PDMS leaching was also a function of the polymer viscosity, with increasing stability achieved upon increasing the viscosity of the PDMS used. The study presented here shows that silicone can leach into a simple system such as water. This emphasizes the need for a careful consideration of the parameters used during the siliconization of the devices that are meant to store aqueous biopharmaceuticals, where the additional presence of surface active species, such as protein and surfactants, can solubilize and promote further silicone oil leaching.

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