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Silicone Migration From Baked-on Silicone Layers. Particle Characterization in Placebo and Protein Solutions

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ABSTRACT

A significant number of therapeutic proteins are marketed as pre-filled syringes or other drug/device combination products and have been safely used in these formats for years. Silicone oil, which is used as lubricant, can migrate into the drug product and may interact with therapeutic proteins. In this study, particles in the size range of 0.2-5 µm and ≥1 µm as determined by resonant mass measurement and micro-flow imaging/light obscuration, respectively, resulted from silicone sloughing off the container barrel after agitation. The degree of droplet formation correlated well with the applied baked-on silicone levels of 13 µg and 94 µg per cartridge. Silicone migration was comparable in placebo, 2 mg/mL and 33 mg/mL IgG1 formulations containing 0.04% (w/v) polysorbate 20. Headspace substantially increased the formation of silicone droplets during agitation. The highest particle concentrations reached, however, were still very low compared to numbers described for spray-on siliconized containers. When applying adequate baked-on silicone levels below 100 µg, bake-on siliconization efficiently limits silicone migration into the drug product without compromising device functionality.
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Introduction

Particle formation in biopharmaceutical drug products is the subject of increasing scrutiny within the biopharmaceutical industry.[1-3] Some levels of particles are ubiquitously found in marketed products, but without evidence of safety risks.[3] Proteinaceous particles may form due to protein aggregation possibly triggered by a wide range of stress conditions such as temperature, freeze/thaw, and agitation in some proteins and formulations.[4-6] In addition, the contact with various materials during manufacturing may result in heterogeneous or nonproteinaceous particles originating, for example, from stainless steel pumps, filters, tubing, or glass containers.[7-10]

The use of pre-filled syringes (PFS) and cartridges as primary packaging is increasing in the healthcare industry. This type of packaging requires a coating, which is mostly using silicone, to ensure the piston easily moves within the device. The presence of silicone becomes a challenge when working with therapeutic proteins due to possible incompatibilities with some proteins and formulations.[11-14] High levels of silicone have been reported to trigger protein aggregation in a few proteins when not appropriately formulated, in particular upon agitation,[15-21] at increased temperatures[22,23] or upon periodically rupture of the silicone oil-water interface.[24] Proteins have a high propensity to interact with surfaces, making them susceptible to adsorption at the liquid-silicone oil interface preferentially in the absence of surfactants in the formulation.[19,20,25-27] However, increased levels of spiked-in silicone did not result in protein aggregation or precipitation during quiescent storage at 4°C and 37°C[20] or room temperature.[25,27]

Abbreviations used: DLS, dynamic light scattering; FNU, formazin nephelometric units; FTIR, Fourier transform infrared; LO, light obscuration; mAb, monoclonal antibody; mAb HC, monoclonal antibody at higher concentration (33 mg/mL); MFI, micro-flow imaging; NTA, nanoparticle tracking analysis; NS, nonsiliconized; PDI, polydispersity index; PFS, pre-filled syringe; RMM, resonant mass measurement; RI, refractive index.

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Other studies suggest that particle level and turbidity increase are most likely due to silicone migration rather than protein instability.[18,28-30]

Several approaches are available to mitigate protein-silicone oil interactions. First, state-of-the-art formulation development, for example, the addition of surfactants, can prevent proteins from adsorption and degradation.[19,20,24-27] Second, optimized siliconization processes with sufficient but limited silicone levels and well-defined silicone distribution can be used.[31] Silicone oil is essential as a lubricant for device functionality to ensure smooth and easy injection.[12,13,32] In conventional spray-on siliconization processes, approximately 0.2 mg to 1 mg silicone oil per container is applied[17,18,23,32-38] compared to bake-on processes, which employ an aqueous diluted silicone emulsion followed by bake-on at approximately 300°C for 10-30 min.[28,39-41] Bake-on siliconization results in limited silicone levels below approximately 0.1 mg per container.[33,42,43] Thereby, bake-on siliconized primary containers present less likelihood to slough off silicone droplets into the formulation compared to spray-on siliconized containers[15,23,34,36] (for further insights into bake-on siliconization processes, please refer to previous publications[31,44,45]). Recently, alternative siliconization methods using cross-linkable silicone have been reported to further prevent transfer of silicone into the product.[15,18,34,36]

This work used a bake-on siliconization process that was previously developed and optimized.[31,45] The study examined the effect of different baked-on silicone levels below 100 μg on the particle formation in cartridges filled with placebo after shaking, expelling, and a combination thereof. Different sampling via expelling and shaking stress as well as different silicone levels may result in entirely different particle concentrations.[34] In addition, the subvisible particle formation was assessed after filling with 2 different concentrations of monoclonal antibody (mAb) solution (2 mg/mL and 33 mg/mL) followed by shaking in the presence and absence of headspace. No single analytical technique is able to cover the entire range from soluble aggregates to visible particles. A number of reviews highlight the selection of appropriate orthogonal techniques including advantages and limitations to monitor aggregates and particulates.[46-52] Therefore, a set of different analytical techniques was applied. Resonant mass measurements (RMM) and micro-flow imaging (MFI) were used to benefit from advances made to discriminate silicone oil droplets from proteinaceous particles.[53-57] As polysorbates are most frequently used as excipients,[58-60] studies were performed in the presence of 0.04% (w/v) polysorbate 20.

Materials and Methods

Materials

Nonsiliconized 5-mL glass cartridges (barrel length, 32 mm; inner diameter, 19 mm; outer diameter, 22 mm), pistons, serum stoppers, and aluminum seals were provided by F. Hoffmann-La Roche Ltd. (Basel, Switzerland). Elastomeric components were coated with fluoropolymer (FluroTec®). Polyethersulfone syringe filters (0.2 μm) were obtained from VWR International GmbH (Darmstadt, Germany). Whatman Anotop 10 (0.02 μm) filters were purchased from GE Healthcare Europe GmbH (Freiburg, Germany). 4R vials and stoppers (both nonsiliconized) were provided by Schott AG (Mainz, Germany) and West Pharmaceutical Services, Inc. (Exton, PA), respectively. Disposable silicone oil-free 1-mL plastic syringes (sample transfer to nanoparticle tracking analysis [NTA] measurement cell) and 22-G, 40-mm-thin wall needles were obtained from Henke-Sass, Wolf GmbH (Tuttlingen, Germany) and Terumo Deutschland GmbH (Wettingen, Germany), respectively.

Chemicals were purchased as follows: 365 35% Dimethicone NF Emulsion and 360 Medical Fluid, 350 cSt, from Dow Corning GmbH (Wiesbaden, Germany); heptane from Riedel-de Haën (Seelze, Germany); both L-histidine monohydrochloride monohydrate and L-histidine from Ajinomoto Europe S.A.S (Louvain-la-Neuve, Belgium); sodium hydroxide standard volumetric solution 1 M from AppliChem GmbH (Darmstadt, Germany); polysorbate 20 from Croda GmbH (Nettetal-Kaldenkirchen, Germany); polystyrene particle standards 0.994 μm from Thermo Scientific Inc. (Waltham, MA); and tergazyme® enzyme detergent from Alconex Inc. (New York, NY). A 33.4 mg/mL IgG1 mAb stock solution in 20 mM histidine buffer pH 5.4 was kindly provided by Roche Deutschland Holding GmbH (Penzberg, Germany).

Bake-on Siliconization Process

Bake-on siliconization was performed on a SVS9061 pilot-scale siliconization unit from Bausch + Ströbel Maschinenfabrik Ilshofen GmbH + Co. KG (Ilshofen, Germany) equipped with an external mixing, 2-fluid nozzle. Optimized spray parameters were established in previous experiments: spray quantity of 4-mg silicone emulsion, fixed nozzle position of 20 mm below the flange, spray pressure of 1 bar, and time for pump dosing of 175 ms.[31] The cartridges were subsequently treated at 316°C for 12 min in a TSQ U03 heat-tunnel from Robert Bosch GmbH (Stuttgart, Germany).

Dow Corning 365 35% Dimethicone NF Emulsion was diluted to 0.6% (w/w) or 3.5% (w/w) with highly purified water to obtain a final baked-on silicone level of 13 ± 3 μg per cartridge and 94 ± 6 μg per cartridge, respectively.[31] Nonsiliconized glass cartridges were used as control for comparison throughout the study.

Preparation of Protein Samples

A 20 mM histidine buffer, pH 6, containing 0.04% (w/v) polysorbate 20 was used as placebo. Solutions of 2 mg/mL (mAb) and 33 mg/mL (mAb HC, higher concentration) in 20 mM histidine buffer, pH 6, and 0.04% (w/v) polysorbate 20 were prepared from stock solutions. After filtration (0.2 μm), mAb concentrations were verified by UV at 280 nm using a NanoDrop 2000 spectrophotometer from Thermo Fisher Scientific Inc. (Waltham, MA) and an extinction coefficient of 1.51 cm^2/mg.

Sample Preparation and Agitation Studies

After bake-on siliconization, the pistons and cartridges were manually assembled. The containers were filled with a target volume of 5.16 mL placebo, mAb, or mAb HC solution and sealed with serum stoppers and aluminum caps. After stoppering, the headspace was calculated as 611 μL assuming a final fluid level of 9.6 ± 0.1 mm from the cartridge top. For experiments without headspace, cartridges were filled and carefully stoppered so that no visible air bubble remained.

The sample solution was expelled from the cartridge through the needle using a material testing instrument TA.XT.plus from Winopal Forschungsbedarf GmbH (Elze, Germany) at a constant displacement speed of 5.6 mm/min over a distance of 17.5 mm (maximum travel distance for the piston within the cartridge barrel), thereby mimicking approximately 3 min injection time.

Agitation was performed at 240 rpm on a 360° horizontal Certomat IS rotator from B. Braun Biotech International GmbH (Melsungen, Germany) for 1 h at 23°C with cartridges positioned horizontally. The horizontal rotation frequency and test duration followed vehicle vibration tests from ISTA 2A and ASTM D 4169-08. Samples were collected by pipetting or decanting through the cartridge orifice after removing the serum stopper.

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