Cross-Linked Silicone Coating: A Novel Prefilled Syringe Technology That Reduces Subvisible Particles and Maintains Compatibility with Biologics

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ABSTRACT: Prefilled syringes (PFSs) offer improvements in the delivery of drugs to patients compared with traditional vial presentations and are becoming necessities in an increasingly competitive biologics market. However, the development of a product in a PFS must take into account potential incompatibilities between the drug and the components of the syringe. One such component is silicone oil, which has previously been suggested to promote protein aggregation, loss of soluble protein, and an increase in the particulate content of injectable formulations. This study evaluated the particulate content in a model buffer system (polysorbate 80/phosphate-buffered saline) after agitation in glass syringes with a novel cross-linked silicone coating. We also evaluated the compatibility of two monoclonal antibodies with these syringes. We report that syringes with this novel coating, compared with standard siliconized syringes, exhibited reduced particle content and enhanced integrity of the lubricant layer as determined by reflectometry, optical microscopy, and time-of-flight secondary ion mass spectrometry measurements, while maintaining the desired functional properties of the syringe and the antibodies' stability profiles as determined by high-performance size-exclusion chromatography. Enhanced integrity of the lubricant coating led to significantly fewer subvisible particles in the liquid formulations, particularly after agitation stresses introduced by shipping of the syringes. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1384–1393, 2014

Keywords: silicone oil; subvisible particles; prefilled syringes; protein formulation; biotechnology; injectables; protein delivery; formulation; cross-linked silicone; XSi™

INTRODUCTION

Prefilled syringes (PFSs) offer advantages in the delivery of drugs to patients compared with traditional vial and disposable syringe configurations. PFSs offer improved dosing accuracy, increased patient compliance and safety, reduced risk of microbial contamination, and reduced overfill. Along with these improvements, however, the development of drug products in PFS presentations imparts its own set of unique challenges,[1,2] particularly in the development of sensitive biologics. Biologics such as cytokines, monoclonal antibodies, nucleic acid-based products, and vaccines are highly complex molecules, and they are subject to a variety of degradation pathways that may impact efficacy and safety.[3–6] The developer of a biologic product by necessity is required to perform extensive formulation and process development studies to obtain a highly pure, effective, safe, and well-characterized product with the typical target of a 2-year shelf-life.[7] A product in a PFS presentation is exposed to more components compared with a product in a traditional vial. Further, compatibility to all components must be demonstrated throughout the entire shelf-life.[1,8] Syringe components such as tungsten,[9] silicone oil,[10] adhesives,[1] leachables from rubber stoppers,[11] and tip caps[12] have all been evaluated and identified as potential sources of incompatibility for biologics.

Silicone oil in particular has received increased attention from formulation scientists in order to understand its compatibility with proteins. Medical grade silicone oil, polydimethylsiloxane (PDMS), is commonly used in pharmaceutical processing for its lubricant properties. It is used to coat glass barrels in PFSs to allow for smooth plunger motion during administration with lower injection forces. Silicone oil is also used to coat stoppers to facilitate handling and insertion into vials.[13] Nonsmooth plunger motions arising from unsiliconized or improperly siliconized components may impact syringe functionality, autoinjector performance (when combined with a PFS), usability and compliance by the end user.[1,14] However, recent studies have related silicone oil to protein aggregation and/or loss of soluble protein in some injectable formulations.[10,12,15–20] Furthermore, silicone oil can slough off the syringe barrel and/or stopper during storage, which may be promoted by the various constituents of the formulation.[12,17,21] These silicone oil droplets may prompt particle formation from protein adsorption to the droplets and coalescence arising from decreased colloidal stability.[8,16–18] The silicone oil droplets themselves along with any silicone oil-induced complexes contribute to a formulation's subvisible particle (SbVP) population.[17,21–24] SbVPs are of potential concern because of limits on particulate matter in

Abbreviations used: CV, coefficient of variation; HPSEC, high-performance size-exclusion chromatography; IgG1, immunoglobulin G type 1; mAb, monoclonal antibody; MFI, microflow imaging; PDMS, polydimethylsiloxane; PFS, prefilled syringe; PS80, polysorbate 80; RH, relative humidity; SbVP, subvisible particle; ToF SIMS, time-of-flight secondary ion mass spectrometry.

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injectable solutions and the possibility that they may elicit an immunogenic response.[22,25,26]

It is currently not possible to generalize the effect of silicone oil on every protein; different proteins may vary in their sensitivity. For example, silicone oil has been shown to have no effect on the purity, structure, stability, or biological activity of the fusion protein albinterferon alfa-2b.[23] On the contrary, the fusion protein abatacept forms visible particles within 20 min of filling into siliconized syringes.[17] Factors such as the properties of the individual protein as well as specific formulation conditions may all have contributing roles. Product handling also has an impact; silicone oil and agitation work synergistically to promote protein aggregation and monomer loss.[15,17,19,20] Protection against agitation-induced stresses is necessary to ensure a robust liquid drug product because agitation is an unavoidable consequence of transportation from the production site to the end user.

To address these challenges in PFS development for biologics that are sensitive to silicone oil and the potential increase in immunogenicity risk raised by SbVPs in solution, a cross-linked silicone coating (XSi™) has recently been developed for achieving significant SbVP reduction in injectable solutions.[21,27] Cross-linking of the silicone surface modifies the physicochemical structure of the lubricant layer, achieving a sharp cross-linking gradient in the region immediately beneath the water–silicone oil interface (Fig. 1). The modified layer acts as a barrier to silicone emulsification, thereby reducing silicone oil migration from the barrel. The underlying, unmodified silicone layer maintains its lubricity, allowing the syringe to retain its desired functionality.[21]

The purpose of this study was twofold. First, using a model buffer system we evaluated the release of subvisible and submicron-sized particles from syringes with the XSi™ coating and compared with other types of PFS container contact surfaces. Second, we evaluated the compatibility of syringes with XSi™ coating with two different immunoglobulin G type 1 (IgG1) monoclonal antibodies and compared the results with those obtained with standard siliconized syringes. The integrity of the lubricant coating in the syringes was evaluated after contact with the monoclonal antibody (mAb) solutions. SbVP levels, mAb purity, and syringe functional performance were measured both after filling and during storage.

Our results show that XSi™ syringes lead to a significant reduction in SbVP levels in solution, mainly via enhanced integrity of the silicone oil lubricant coating. The XSi™ syringes also maintained their functional performance, and there were no changes to each mAb's stability profile as determined by high-performance size-exclusion chromatography (HPSEC).

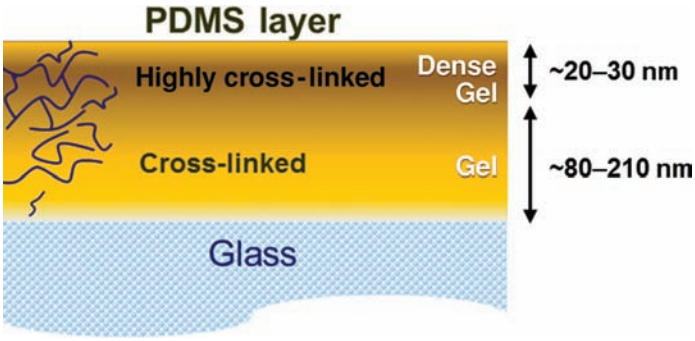

Figure 1. Schematic representation of the cross-linked silicone (XSi™) coating.

MATERIALS AND METHODS

Materials

One milliliter long SCF (sterile, clean, ready to fill) glass syringes (Hypak™, 29 $G^{1/2''}$, RNS BD260 Black, Ultra low tungsten; BD Medical—Pharmaceutical Systems, Le Pont de Claix, France) were used for mAb compatibility evaluation. Syringes with two different lubrication levels were prepared: 0.25 and 0.4 mg/barrel DC360 PDMS by diving nozzle process. XSi™ syringes were prepared following siliconization via a process proprietary to BD (Neopak™ XSi™, 29 $G^{1/2''}$, RNS BD260 Black, Ultra low tungsten; BD Medical – Pharmaceutical Systems). BSCF™, 1-mL long stoppers were used (4023 West-Daikyo SI1000; BD Medical—Pharmaceutical Systems). All syringe batches met silicone oil targets prior to use.

For evaluation of particle release in a model buffer system among different PFS types, two additional syringes were evaluated. Unsiliconized syringes were evaluated using 1-mL long SCF™ glass syringes (Hypak™, 29 $G^{1/2''}$, RNS BD260 Black, Ultra low tungsten; BD Medical – Pharmaceutical Systems) in the absence of any lubricant. Baked siliconized syringes were 1-mL long SCF™ glass syringes (SCF1MLL RF PRTCFM27 BAKED SIL, no needle; BD Medical—Pharmaceutical Systems).

Two model IgG1s, termed mAb A and mAb B, were used for the compatibility study. Each was produced and purified at MedImmune (Gaithersburg, Maryland). mAb A (~148 kDa) was formulated at 100 mg mL^{-1} in histidine buffer, pH 6, with sodium chloride and polysorbate 80 (PS80) as excipients. mAb B (~147 kDa) was formulated at 150 mg mL^{-1} in histidine buffer, pH 6, with a disaccharide and PS80 as excipients. The concentration of each mAb was verified using experimentally determined coefficients of 1.61 and 1.53 mL mg^{-1} cm^{-1} for mAb A and mAb B, respectively. Each mAb's formulation buffer (without protein) was also filled into syringes as buffer-only samples.

Comparison of Particle Release Among PFS Technologies

Particle release in XSi™ syringes was compared with that in other PFS technologies. Syringes were filled with 0.02% (w/v) PS80 in 10 mM phosphate-buffered saline (PBS; Sigma–Aldrich, St. Louis, Missouri) in a laminar flow hood. Stoppers were automatically inserted by a vacuum stopper placement unit. The filled syringes were then placed on a 360° vertical rotator apparatus (Grant-Bio PTR60; Keison International, Chelmsford, UK) and agitated for 2 days at 60 rpm. After agitation, the stoppers were carefully removed and the samples were analyzed as described below by microflow imaging (MFI) for particles in the 2–100 μm size range and by nanoparticle tracking analysis (Nanosight, Amesbury, UK), resonant mass measurement (Archimedes, Affinity Biosensors, Santa Barbara, CA), and image analysis (Occhio, Angleur, Belgium) for particles in the 0.2–1 μm size range. All data were normalized with respect to the total particle counts per milliliter measured in standard siliconized syringes sprayed with 0.4 mg silicone oil.