Functional Evaluation and Characterization of a Newly Developed Silicone Oil-Free Prefillable Syringe System

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ABSTRACT: The functionality of a newly developed silicone oil-free (SOF) syringe system, of which the plunger stopper is coated by a novel coating technology (i-coating™), was assessed. By scanning electron microscopy observations and other analysis, it was confirmed that the plunger stopper surface was uniformly covered with the designed chemical composition. A microflow imaging analysis showed that the SOF system drastically reduced both silicone oil (SO) doplets and oil-induced aggregations in a model protein formulation, whereas a large number of subvisible particles and protein aggregations were formed when a SO system was used. Satisfactory container closure integrity (CCI) was confirmed by means of dye and microorganism penetration studies. Furthermore, no significant difference between the break loose and gliding forces was observed in the former, and stability studies revealed that the SOF system could perfectly show the aging independence in break loose force observed in the SO system. The results suggest that the introduced novel SOF system has a great potential and represents an alternative that can achieve very low subvisible particles, secure CCI, and the absence of a break loose force. In particular, no risk of SO-induced aggregation can bring additional value in the highly sensitive biotech drug market. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:1520–1528, 2014

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INTRODUCTION

The recently increased interest in prefilled syringes (PFS) is largely driven by many advantages against traditional ampoules and vials, such as allowing quick and accurate dosing, minimizing dosing errors, reducing the risk of biological contamination, enhanced convenience and ease of use, preventing of overfill, and so on. On increasing number of available biological drugs, the demand for the use of PFS has considerably increased in recent years.

Silicone oil (SO) is widely used as a lubricant in syringes to ensure a smooth gliding behavior of the plunger inside the barrel. Furthermore, siliconization effectively prevents the plunger stoppers from sticking together during the material shipping and manufacturing process. It is also important to minimize the mechanical force when the plunger stoppers are inserted into a barrel using a mechanical stoppering machine. Siliconization is therefore essential to the process capability of the SO-lubricated syringe. However, it is known that the use of SO-coated syringes leads to difficulties in case of some silicone-sensitive drugs, such as protein-based drugs. For example, several reports in the 1980s implicated that the ingress of SO from disposable syringes caused aggregation of human insulin.[1–5] Researchers continue to seek how SO can accelerate the intermolecular interactions of proteins, and stability studies revealed that the oil could negatively affect the chemical and physical stability of the protein formulation, thereby causing a loss of soluble proteins.[6,7] Additional works have been performed to assess the effects of ionic strength and the type of surfactants that can be used to minimize the risk of a SO-induced aggregation.[8–10]

Silicone oil-induced aggregation has now become one of the most frequently discussed subjects in the field of PFS, particularly for developers of highly sensitive biotech drugs.[6,11,12] Once SO detaches from the inner wall of the barrel, oil droplets are formed that contribute to the population of subvisible particles. The levels of visible and subvisible particles have become critical also to the quality of drug products in PFS.[13–15] To mitigate the risk, the reduction of the SO quantity may be one of the options to be considered, but this may not be adequate because siliconization is essential to ensure the functionality of the syringe over the shelf life of the product, and even if the quantity of SO is reduced, the risk of SO-induced aggregation cannot be eliminated completely.

Under such circumstances described above, the demand for the SO-free (SOF) system has been rising, and various technologies have been proposed so far.[16] Most of them are coating technologies in which the surface of the barrel and/or plunger stopper is coated with a lubricious, compatible, and physicochemically inert material. In response to this unmet need, Terumo created an innovative coating technology, which resulted in the successful introduction of an SOF system for polymer-based PFS in 2005 within the Japanese market that is still supplied in the market today.

Through continued research and development, Terumo has introduced the next generation of SOF coating technology called i-coating™ for use on plunger stoppers. By using this

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technology, novel SOF system for prefillable syringes can be accomplished.

The purpose of the present study is to characterize the functionality of this novel SOF system by comparing it with current SO system. In this paper, the coated surface was characterized by means of scanning electron microscopic (SEM) observations, FTIR analysis, and X-ray photoelectron spectroscopy (XPS), and the influences on the generation of subvisible particles, container closure integrity (CCI), and break loose gliding forces as important attributes of PFS were assessed.

MATERIALS AND METHODS

Materials

PLAJEX™ syringe [Polymer based prefillable syringe, 1 mL long staked needle (27G)] (SOF syringe system) was provided by Terumo Corporation (Tokyo, Japan), which is a newly developed prefillable syringe with a polymer barrel made of cyclic olefin polymer and a butyl rubber plunger stopper coated by use of the i-coating™ technology (a proprietary coating). The corresponding PLAJEX™ syringe lubricated by SO with an uncoated plunger stopper (SO system for comparison) was also provided by Terumo Corporation. A butyl rubber sheet of 1 mm in thickness was obtained from Asahi Rubber Inc. (Saitama, Japan). Using the i-coating™ technology, the coated butyl rubber sheet was provided by Terumo Corporation. As a reference sample, SO-coated butyl rubber sheet was also provided by Terumo Corporation. L-Asparaginase (Asp) was purchased from Prospec-Tany TechnoGene Ltd. (Rehovot, Israel); human IgG was purchased from Equitech-Bio Inc. (Kerrville, Texas, USA); albumin from bovine serum (BSA) and lysozyme from chicken egg white (Lyso) were purchased from Sigma–Aldrich Company LLC., (St. Louis, MO, USA), respectively. Triptic soy agar and triptic soy broth (TSB) were purchased from Becton, Dickinson and Company (Franklin lakes, NJ, USA). Isotonic sodium chloride solution and commercially available saline solution of Japanese Pharmacopoeia grade (JP grade) were obtained from Terumo Corporation. Water for injection (20 mL) was JP grade and purchased from Otsuka Pharmaceutical Company Ltd., (Tokyo, Japan). Crystal violet and all buffer salts (sodium phosphate monobasic, sodium phosphate dibasic, and sodium chloride) were purchased from Kanto Chemical Corporation (Tokyo, Japan). All other chemicals and reagents were of analytical grade.

Scanning Electron Microscopy

Scanning electron microscopic observations were performed using a microscope model KEYENCE VE8800 (Tokyo, Japan) to assess the integrity of the coating layer of the plunger stopper. The surface and the cross-section of the coated and uncoated plunger stoppers were observed with magnifications of $\times 300$ or $\times 1000$. To produce a cross-section, a sample was cut vertically by a razor. After platinum was sputtered, the top surfaces and cross-sections of the samples were observed at an acceleration voltage of 1.7 kV.

Fourier Transform-Infrared Spectroscopy

The top surface of the uncoated and coated plunger stopper was analyzed using an FTIR spectrometer (Spectrum100; PerkinElmer, Wellesley, Massachusetts) equipped with a universal attenuated total reflectance (ATR) sampling accessory. ATR–FTIR spectra were recorded at a resolution of 4 cm^{-1} and 16 scans per specimen were averaged in a wavenumber range from 650 to 4000 cm^{-1}.

X-Ray Photoelectron Spectroscopy

The top surface of the coated plunger stopper was analyzed by means of XPS (Axis-NOVA, Kratos, Manchester, UK) using monochromated Al-Kα (1486.6 eV) X-ray radiation. The X-ray tube was operated at 15 kV and 20 mA. The take-off angle between the sample plane and the axis of the analyzer was 90°. A pass energy of 80 eV was chosen for the acquisition of a survey spectrum (0–1000 eV). The pressure was maintained below 10^{-8} Pa during the measurements.

Protein Aggregation Study

Ten thousand units of Asp were dissolved in 2 mL of water for injection (JP grade). After complete dissolution, the syringes were filled with 1.0 mL of the Asp solution and stopped with plunger stoppers leaving a predetermined headspace of 0.4 mL. The syringes were also filled with 1.0 mL of pure water for injection as reference for the protein aggregation study. After filling, the syringes were shaken in a shaker (SR-I; TAITEC Company Ltd., Saitama, Japan) for 30 min at 250 rpm at room temperature. Immediately after shaking, aliquots of the sample solution were drawn out through a needle by actuation of the plunger stopper and analyzed for particle concentration by micro-flow imaging (MFI). DPA4200 (Brightwell Technologies Inc., Ottawa, Canada) was used for the measurement of subvisible particles. The number of subvisible particles whose equivalent circular diameter is larger than 5 μm was analyzed in this study. Moreover, to obtain information about particle shape, an aspect ratio (AR) filter was employed to distinguish circular ($AR \geq 0.85$) and noncircular particles ($AR < 0.85$). Here, particles having $AR \geq 0.85$ and $AR < 0.85$ are regarded as SO droplets and SO-induced protein aggregates, respectively, according to previous studies.[17,18] In addition, IgG, BSA, and Lyso were dissolved at 1 mg/mL in a buffer (10 mM Na_2HPO_4, 130 mM NaCl, pH 7.2) and used.[6] Subvisible particles of these protein solutions were also measured in the same manner as described above.

Dye Penetration Study

To assess the CCI of the syringes, a dye penetration study was conducted. One milliliter of water was filled into the syringes and the headspace of the syringes was adjusted to predetermined distances (0.5, 0.75, 1.0, and 1.35 mm) by pushing the plunger stopper down. A small amount (0.15 mL) of 1.0% crystal violet aqueous solution was then placed into the space between the plunger stopper and the flange. The sample syringes were vertically placed in a decompressed chamber (adjusted at −19.6 kPa with respect to normal atmospheric pressure). After 2 h, the water in the syringes was carefully drawn out through a needle and photometrically analyzed to determine the dye concentration using a spectrophotometer SHIMADZU UV-2450 (Kyoto, Japan).

Microorganism Penetration Study

The study was performed according to the method proposed by the pharmaceutical inspection convention.[19] In addition to the intact PLAJEX™ syringe, a PLAJEX™ syringe with a pinhole (size of about 8 μm) on the pathway of the barrel was