Research

Syringe Siliconization Process Investigation and Optimization

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ABSTRACT: The interior barrel of the prefilled syringe is often lubricated/siliconized by the syringe supplier or at the syringe filling site. Syringe siliconization is a complex process demanding automation with a high degree of precision; this information is often deemed "know-how" and is rarely published. The purpose of this study is to give a detailed account of developing and optimizing a bench-top siliconization unit with nozzle diving capabilities. This unit comprises a liquid dispense pump unit and a nozzle integrated with a Robo-cylinder linear actuator. The amount of coated silicone was determined by weighing the syringe before and after siliconization, and silicone distribution was visually inspected by glass powder coating or characterized by glide force testing. Nozzle spray range, nozzle retraction speed, silicone-coated amount, and air-to-nozzle pressure were found to be the key parameters affecting silicone distribution uniformity. Distribution uniformity is particularly sensitive to low-target silicone amount where the lack of silicone coating on the barrel near the needle side often caused the syringes to fail the glide force test or stall when using an autoinjector. In this bench-top unit we identified optimum coating conditions for a low silicone dose, which were also applicable to a pilot-scale siliconization system. The pilot unit outperformed the bench-top unit in a tighter control (standard deviation) in coated silicone amount due to the elimination of tubing flex. Tubing flex caused random nozzle mis-sprays and was prominent in the bench-top unit, while the inherent design of the pilot system substantially limited tubing flux. In summary, this bench-top coating unit demonstrated successful siliconization of the 1 mL long syringe with ~0.2 mg of silicone oil using a spraying cycle also applicable to larger-scale siliconization.

KEYWORDS: Prefilled syringe, Siliconization, Dive-in nozzle spray, Silicone amount, Silicone distribution, Glide force, Glass powder testing

LAY ABSTRACT: Syringe siliconization can be considered a well-established manufacturing process and has been implemented by numerous syringe providers. However, its technical details and associated critical process parameters are rarely published. The purpose of this study is three-fold: (1) to reveal design details of a bench-top siliconization unit, (2) to identify critical process parameters and determine their optimum range to provide consistent and even silicone coating, and (3) to demonstrate the applicability of the optimum process condition derived from the bench-top unit to a pilot siliconization unit. The outcomes of this study will benefit scientists and engineers developing pre-filled syringe products by helping them to better understanding silicone spray coating principles and their relationship to siliconization processes in a large-scale manufacturing setting.

Introduction

Pre-filled syringes are now the primary container of choice for most parenteral drug delivery systems, mainly because they are safe and user-friendly (1). Manufacturing a pre-filled syringe product is a complex process (2–4), including liquid formulation preparation (thawing, compounding, sterile-filtration, etc.), component assembly (syringe, stopper, needle, and needle shield), syringe fill, stopper placement, labelling, packaging, and so on. Some device components are lubricated (or *siliconized,* as silicone oil is the industry standard and a Food and Drug Administration–approved lubricant), particularly the interior barrel of the syringe to ensure ease of syringe performance and consistency of the injection force (3–5). Siliconization can be performed by the syringe manufacturer in the ready-to-fill (or *nest* or *tub*) format or in the syringe fill facility prior to filling in the bulk configuration (3).

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There are three types of silicone fluid, or polydimethylsiloxane (PDMS), available for syringe/cartridge lubrication: non-reactive silicone oil (e.g., Dow Corning [DC] 360 Medical Fluid available in five viscosities), non-reactive silicone emulsion (e.g., DC 365 35% Dimethicone NF Emulsion), and reactive (curable) silicone fluid (e.g., DC MDX5-4159 Medical Grade Dispersion). After silicone application, a high-temperature "baking" process is required for silicone emulsion and reactive silicone fluid for depyrogenation, or curing. The non-reactive silicone oil doesn't require the post-application baking process as DC 360 are tested for bacterial endotoxins and certified to meet National Formulary/European Pharmacoepeia specifications (6). Regardless of the silicone fluid type, silicone applications are commonly performed by wipe-on or spray coating (5), where the fluid is atomized into a mist via a nozzle and deposited on the coated surface. Thus, siliconization relies on three mechanisms: accurate dosing, controlled atomization, and precise nozzle movement. Two-fluid atomization of viscous silicone fluid via high-pressure air is currently the best option for producing fine droplets. A precision pump is used to accurately deliver a minute amount of fluid for atomization. The nozzle needs to travel at a controlled speed inside the syringe barrel to coat its inner surface evenly. These three mechanisms need to coordinate perfectly to provide a fixed dose of fluid distributed uniformly across the internal surface of the syringe. Despite the fact that automated, high-speed manufacturing processes have been established for many years to produce siliconized syringes, our literature search failed to find publications detailing siliconization process development. Instead, most publications focused on formulation and stability considerations as the result of silicone-protein interactions (4, 7–9).

The objective of this study is to develop and optimize a bench-top siliconization system with a focus of assessing the effect of critical parameters on coating amount and distribution uniformity. This bench-top unit was also compared with a semi-automated, pilot-scale siliconization system to understand how system design affects siliconization performance.

Materials and Methods

All experiments in this study employed 1.0 mL long 27G ½″ staked needle syringes to be coated with silicone oil (DC 360 Medical Fluid, 1000 cSt) using a bench-top siliconization system (Figure 1) or a semi-automated pilot scale unit. Equipment and materials used in this study are tabulated in Table I.

Bench-Top Siliconization System—Spraying Unit

The siliconization bench-top unit was assembled and tested by Volo Technologies (Roseville, CA). This setup (Figure 1a) integrates a spraying unit with a robot system controlling nozzle movement. The spraying unit (Figure 1b) consists of an IVEK Sonicair nozzle, a piston pump, a pump linear actuator, a heater module, and a Digisonic controller, while the robot system is composed of a Robo-cylinder linear actuator and its controller. A high-precision, ceramic positive displacement pump controlled by a linear actuator for dosing delivers silicone oil to the Sonicair nozzle set. The nozzle set includes a nozzle head and a nozzle (enlarged section of Figure 1b). The head contains ports to receive silicone oil, air, and a heat cartridge. The nozzle itself, based on a two-fluid atomization mechanism, features two concentric tubes with silicone oil flowing through the inner tube and high-pressure air flowing between the two tubes. The oil and the air meet at the tip of the nozzle for mixing, and the mixture is sprayed via a 0.5 mm orifice into a cone-shaped mist (Figure 1c). Nozzle air is supplied via in-house compressed air and controlled by a pressure gauge. The same air source controlled by a separate pressure gauge is fed to the silicone oil reservoir (5 psi was used throughout this study), which precedes the piston pump module. The nozzle head can be equipped with a heating element as an optional feature. A heat cartridge (Firerod®, Watlow, St. Louis, MO), when inserted into the port on the nozzle head, can heat the nozzle head to a pre-set temperature (in the range of 25 to 125 °C). The temperature of the nozzle will rise due to heat transferred from the nozzle head. Nozzle air can be simultaneously heated by a heating tube inserted between the pressure gauge and the nozzle head and controlled by a separate heat controller.

The pump module is a piston/cylinder arrangement providing positive displacement. The actuator module selectively rotates and reciprocates the ceramic piston via a coupling at one end, and the piston incorporates a slit that provides a valving function at the other end. Initially the piston flat aligns with the silicone oil intake port and then retracts to fill the cylinder with liquid. The piston rotates 180° with the flat facing the discharge port and then pushes forward to force the

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TABLE I
Equipment and Materials Used in the Study

Equipment	Supplier/Model
Balance	Mettler Toledo AG 204 (Columbus, OH)/AG135
Two fluid nozzle (5 mm OD and 90 mm length)	IVEK Corp. (North Springfield, Vermont)/Sonicair
Ceramic positive displacement piston pump and controller	IVEK Corp. (North Springfield, Vermont)/Micro linear pump module & Linear actuator module
Pump controller module (Micro linear actuator)	IVEK Corp. (North Springfield, Vermont)/Digispense 3020
Robo-cylinder linear actuator	IAI America (Torrence, CA)
PLC/HMI controller	Omron American (Schaumburg, IL)
Nozzle heater	Watlow (St. Louis, MO)/Firerod®
Nozzle heater controller	Red Lion Controls (York, PA)/Model T48
Instron force measuring device	Instron (Grove City, PA)/Model 5542
Vent wire stoppering tool	Becton Dickinson (Franklin Lakes, NJ)/Custom tool
Semi-automatic syringe washer	Bausch Advanced Technology (Clinton, CT) Type 303 Washer
Materials	**Supplier/Model**
1 mL-Long syringe with 27G × ½″ staked needle	Becton Dickinson (Swedesboro, NJ)/ Hypak Type 1 glass syringes (Lot # 082111)
Tefzel tubing (1/8″ OD, 1/16″ ID)	Upchurch Scientic (Oak Harbor, WA)
Plunger stopper	West Pharmaceuticals (Lionville, PA) W4023/FLT (Lot # 0000122330)
Polystyrene plunger rod	Becton Dickinson (Bridgeport, NJ)/ Plunger rod for 1mL Long (Lot # 44386)
Silicone fluid	Dow Corning (Midland, MI)/Dow 360 Medical Fluid, 1,000 cSt (Lot # 0005938393)

required amount of oil through the discharge port. The piston rotates 180° again back to the initial position to complete the dispense cycle. The height that the piston travels determines the volume of the oil to be sprayed.

Robotic Movement Control

The Robo-cylinder linear actuator provides the diving action for the nozzle set (Figure 1a & b). The whole nozzle set moves up and down per the commands from the Volo Controller. This controller combines the function of a programmable logic controller (PLC) and a human machine interface (HMI). The siliconization bench-top unit can be run manually or programmed to run an automatic siliconization cycle where the nozzle dives upward into the syringe and sprays silicone while retracting. The Volo Controller is interfaced with the Digispense Controller to send signals to begin and end pumping the oil. To enable the function of controlling nozzle movement such as the dive-in position, the spray position, the spray rate, and the acceleration/deceleration, various setpoints need to be entered on Volo HMI and Digispense. The procedure of preparing a worksheet for setpoint entry is detailed in the Appendix.

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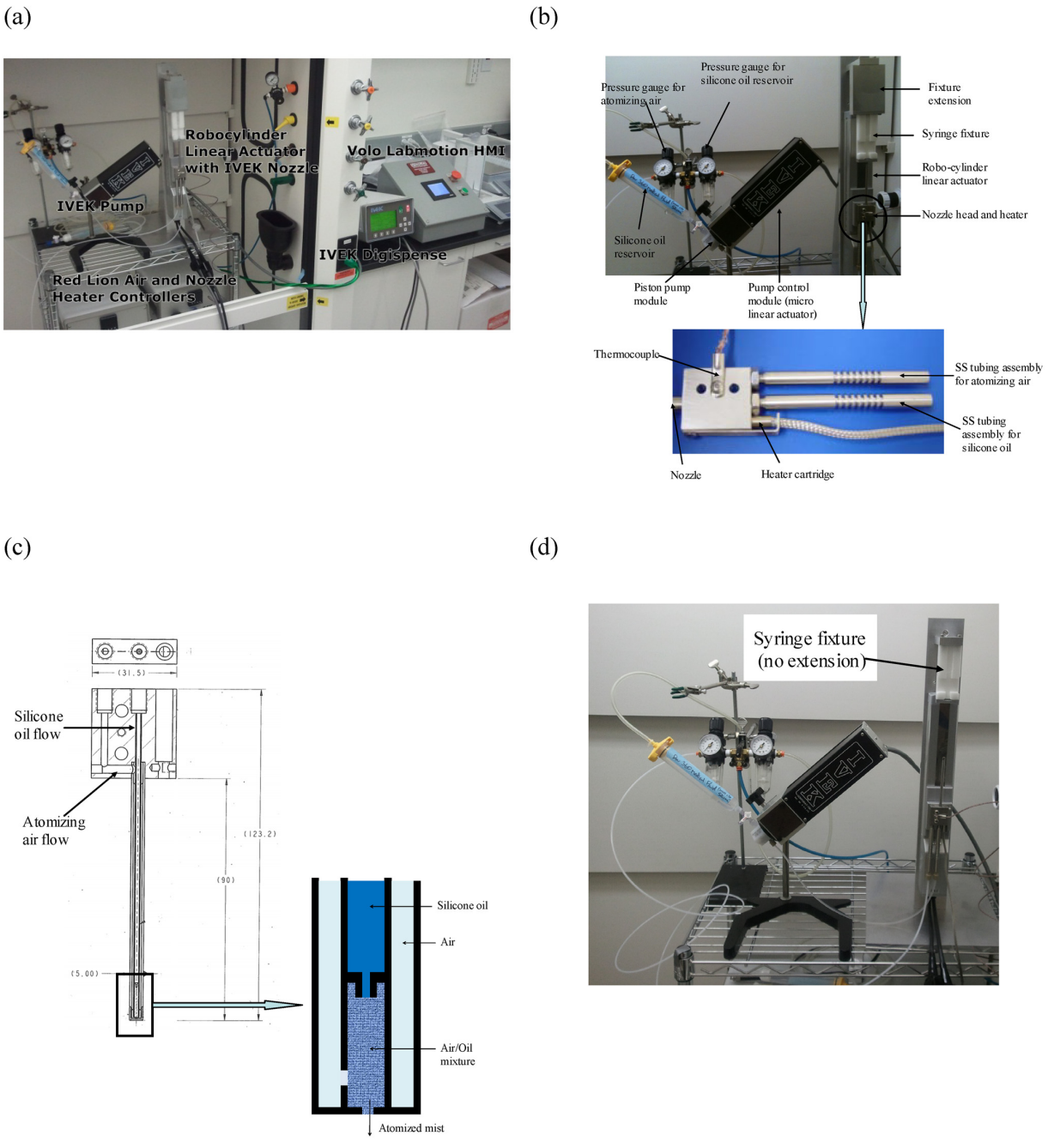

Figure 1

(a) The entire bench-top siliconization system; (b) detailed representation of the pump module, the nozzle set, and syringe fixture and station; (c) detailed graphic representation of the nozzle design and the two-fluid atomization mechanism; and (d) syringe fixture station without the extension.

Pilot-Scale Siliconization Station

The semi-automated syringe washing/siliconization equipment was designed and assembled by Bausch Advanced Technology (Clinton, CT). This pilot-scale equipment is equipped with an Allen Bradley touch screen HMI that provides operators with full control of machine settings to wash, air-dry, and siliconize sy-

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ringes. Syringes are fed manually at the in-feed station with needle pointing downward. The in-feed scroll indexes and transports the syringes into individual grippers. The gripper then rotates and inverts the syringe 180°, with needle pointing upward. The syringe is then transported through 16 gripper stations that include three washing stations, five drying stations, one barrel siliconization station, and one needle siliconization station (a feature not relevant to this study). The mechanism of siliconization is very similar to the bench-top silicone oil spraying unit described above.

Both pilot-scale and bench-top units utilize the same IVEK Sonicair spraying nozzle combined with a high-precision, ceramic positive displacement pump and heating elements. Customized setpoints, such as silicone dosing amount, nozzle/air temperatures, and spray nozzle movement/positions can be controlled via the washer HMI. A dive-in siliconization motion is achieved by the use of a cam fixture, which works similarly to the linear actuator in the bench-top unit. However, the pilot-scale siliconization station features a synchronized movement of the pump and the nozzle, as both are physically attached to the cam fixture. This feature enhances siliconization performance and will be discussed in the Discussion Section.

Silicone Amount

The amount of silicone oil applied on each syringe was determined by using a high-precision digital balance (Mettler Toledo AG 204). Empty syringes were weighed before and after the siliconization process. The silicone oil quantities were measured by calculating the differences between the two values.

Fixed Nozzle Siliconization Testing

Syringes (n = 5) were sprayed with 0.5 mg of silicone oil using an air-to-nozzle pressure of 15 psi at three fixed positions, 5 mm, 20 mm, and 35 mm past the flange. Each siliconized syringe was then coated with glass powder and visually inspected.

Silicone Distribution (Glass Powder Method)

A Schott glass powder 8250 (Grain Size K1, d_{50} = 30 μm ± 10 μm, $d_{99} \leq 150$ μm) was used to visualize and assess silicone distribution uniformity in the inner barrel of a syringe. This specific glass powder was designed to only stick to glass surfaces coated with silicone oil. Approximately 150 mg of glass powder was poured into the open end of the syringe, which was subsequently covered with parafilm. The syringe was then tilted, tapped, and shaken manually for 30 s while in a horizontal position to distribute powder along the axis of the barrel. Subsequently, the used powder was discarded. With the open end pointing downward, the syringe was tapped gently against a flat surface for up to 25 times to remove any excess powder. Coated syringes were then inspected visually for homogeneous powder distribution. Any empty gap greater than 5 mm was defined as unacceptable.

Silicone Distribution (Glide Force Method)

High-speed force testing was performed as a quantitative assay to gauge silicone distribution uniformity within the inner barrel of the syringe. A plunger stopper (W4023/FLT, West Pharmaceutical, Lionville, PA) was inserted into the empty, post-siliconized syringe approximately 8 mm inward (measured from the back of the syringe flange to the back of a stopper) using a vent wire stoppering tool (Becton Dickinson, Franklin Lakes, NJ). Next, a polystyrene plunger rod was carefully threaded into the plunger stopper. A material testing system (model 5542, Instron, Grove City, PA) with a load cell was used to apply a steady compression rate, and the gliding force profile was then analyzed for silicone coating consistency and variation per an internal protocol.

Results and Discussion

Two coating experiments were initially performed to confirm the effect of fixed-position spray coating on distribution uniformity and coated silicone amount. The experimental set-up follows Figure 1d, where the syringe fixture extension was not used.

Effect of Fixed-Position Spray on Coating Distribution Uniformity

Figure 2a–c shows distribution uniformity results for the fixed-position spray coating at 5, 20, and 35 mm past the flange, respectively. Spraying near the flange (5 mm) resulted in silicone deposition mostly on the flange side of the barrel and leaving the barrel on the needle side uncoated. When the nozzle was deeper into the syringe (20 mm), the middle section of the barrel was coated. Further into the syringe at 35 mm past the flange, coating occurred primarily at the needle side. This finding suggests that fixed-position spray yields uneven distribution and that the nozzle

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