European Journal of Pharmaceutics and Biopharmaceutics 104 (2016) 200–215

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Optimization of the bake-on siliconization of cartridges. Part I: Optimization of the spray-on parameters

Stefanie Funke [a], Julia Matilainen [b], Heiko Nalenz [b], Karoline Bechtold-Peters [b], Hanns-Christian Mahler [b,1], Wolfgang Friess [a,*]

[a] Ludwig-Maximilians-Universität München, Department of Pharmacy, Pharmaceutical Technology and Biopharmaceutics, 81377 München, Germany
[b] F. Hoffmann-La Roche Ltd, Pharmaceutical Development & Supplies, PTD Biologics Europe (PTDE-P), 4070 Basel, Switzerland

ARTICLE INFO

Article history:
Received 19 February 2016
Revised 4 May 2016
Accepted in revised form 9 May 2016
Available online 10 May 2016

Keywords:
Cartridge
FTIR
Functionality
3D-Laser Scanning Microscopy
Siliconization
Spray process
Silicone distribution
Silicone layer thickness

ABSTRACT

Biopharmaceutical products are increasingly commercialized as drug/device combinations to enable self-administration. Siliconization of the inner syringe/cartridge glass barrel for adequate functionality is either performed at the supplier or drug product manufacturing site. Yet, siliconization processes are often insufficiently investigated. In this study, an optimized bake-on siliconization process for cartridges using a pilot-scale siliconization unit was developed. The following process parameters were investigated: spray quantity, nozzle position, spray pressure, time for pump dosing and the silicone emulsion concentration.

A spray quantity of 4 mg emulsion showed best, immediate atomization into a fine spray. 16 and 29 mg of emulsion, hence 4–7-times the spray volume, first generated an emulsion jet before atomization was achieved. Poor atomization of higher quantities correlated with an increased spray loss and inhomogeneous silicone distribution, e.g., due to runlets forming build-ups at the cartridge lower edge and depositing on the star wheel. A prolonged time for pump dosing of 175 ms led to a more intensive, long-lasting spray compared to 60 ms as anticipated from a higher air-to-liquid ratio. A higher spray pressure of 2.5 bar did not improve atomization but led to an increased spray loss. At a 20 mm nozzle-to-flange distance the spray cone exactly reached the cartridge flange, which was optimal for thicker silicone layers at the flange to ease piston break-loose. Initially, 10 µg silicone was sufficient for adequate extrusion in filled cartridges. However, both maximum break-loose and gliding forces in filled cartridges gradually increased from 5–8 N to 21–22 N upon 80 weeks storage at room temperature. The increase for a 30 µg silicone level from 3–6 N to 10–12 N was moderate. Overall, the study provides a comprehensive insight into critical process parameters during the initial spray-on process and the impact of these parameters on the characteristics of the silicone layer, also in context of long-term product storage. The presented experimental toolbox may be utilized for development or evaluation of siliconization processes.

1. Introduction

Pre-filled syringes (PFS) and drug/device combination products equipped with cartridges are increasingly used to enable self-administration of parenteral medications. They are safe, less prone to contamination, user-friendly and often require less overfill [1–5].

Usually, the primary container is lubricated with silicone oil to reduce the friction between the container wall and the piston, which in turn facilitates good injectability and function and reliable dosage with sufficient precision during injection [6–8]. Of note, functionality is still one of the major concerns for drug/device combination products [9,10].

Siliconization is an established unit operation. Typically, two different siliconization procedures are used referred to as spray-on and bake-on siliconization [11,12].

Abbreviations: 3D-LSM, 3D-Laser Scanning Microscopy; ALT, average layer thickness; B + S, Bausch + Ströbel; FTIR, fourier transform infrared spectroscopy; LOQ, limit of quantification; PFS, pre-filled syringes; VSI, vertical scanning interferometry.

* Corresponding author.
E-mail address: Wolfgang.Friess@lrz.uni-muenchen.de (W. Friess).
[1] Current address: Lonza AG, Drug Product Services, 4052 Basel, Switzerland.

http://dx.doi.org/10.1016/j.ejpb.2016.05.007
0939-6411/

Staked-in needle syringes, where an adhesive (glue) is used to embed a needle into the fluid path, are processed via spray-on siliconization using silicone oil. Bake-on siliconization however, is not applicable to staked-in needle PFS due to the low heat resistance of the adhesive (glue) needed to fix the needle into the fluid path. Polydimethylsiloxanes, e.g., Dow Corning 360 Medical Fluid [13] with viscosities ranging from about 1000 cSt [14] to 12,500 cSt [15], are most commonly applied as lubricant, but other linear or branched polydialkylsiloxanes such as polydipropylsiloxane, and polydihexylsiloxane are possible alternatives [15]. Due to the viscosity of silicone oil, it may be difficult to precisely deliver a small amount of the lubricant [16]. Spray-on silicone layers exhibit individual plaque-like and micro-droplet structures [10,17,18] and an uniform homogeneous coating is most likely not readily formed [19]. Therefore, in spray-on siliconization processes most commonly higher silicone levels of 0.2–1 mg/barrel are applied [8,13,16–18,20–23] compared to <0.1 mg/barrel for bake-on siliconization processes, where heat promotes the formation of a homogeneous silicone layer [20,24,25]. To overcome these drawbacks, silicone oil could be applied as mixture with volatile organic solvents, e.g., alkanes, alkenes or with low viscosity liquid silicones (0.1–200 cSt). After evaporation of the solvent or low viscosity silicone, the high viscosity silicone remains as lubricant on the glass surface [19,26,27].

Luer-tip syringes with open syringe cones are usually applying bake-on siliconization, using a (diluted) silicone emulsion, e.g., Dow Corning 365 35% Dimethicone NF Emulsion, followed by a high temperature process at approximately 300 °C to remove the emulsion water and to decompose emulsion stabilizers as well as concomitant pyrogens [28–31]. Before administration, a needle can be attached to the luer tip [8], following respective instructions for use of the pharmaceutical manufacturer. Cartridges as part of delivery systems are combined with separate pen needles, and can therefore also be bake-on siliconized. The absolute spray amount of a diluted silicone emulsion can be precisely adjusted, thereby providing accurate control of the total silicone oil content. The thin, but sufficient baked-on silicone layer assures functionality during storage and minimizes silicone migration into the drug product [16,18,21,26,32]. Although different silicone levels are likely of less relevance for patient safety, it may also be beneficial for few, very silicone-sensitive protein therapeutics [12,21].

Recently, alternative coating methods utilize cross-linked silicone to further prevent silicone leaching from the barrel interior [16,18,23,26,27,33]. In addition, silicone-oil free systems are being promoted. These techniques include lubricious, biocompatible coatings for plunger stoppers, which may enable adequate extrusion performance in silicone oil free syringes, e.g., fluoropolymer coatings (FluroTec®) or proprietary i-coating™, often in combination with polymer based syringes (Plajex™, CrystalZenith®) [34–36]. Studies suggest a great potential of these systems for highly sensitive protein therapeutics with low protein aggregate and subvisible particle levels, but suitability has still to be confirmed with more systematic investigations. Additionally, extractables/leachables, oxidation and packaging sterilization may be among the challenges to be overcome [22].

So far, siliconization media are well-characterized, whereas the siliconization process itself varies from a dipping, spray-on, wipe-on to a washing procedure of the component to be siliconized [15,19,27]. Technical aspects of a spray-on process using automated siliconization units were described in the literature [13,37], but are often considered as proprietary know-how and therefore rarely published. Consequently, there is a high variability in the silicone content, distribution and leaching from individual PFS [24,38], which increases the need for a clearly defined siliconization processes. As the demand for PFS and drug/device combination product increases, the understanding and optimization of siliconization processes become even more relevant. Automated siliconization units precisely regulate the spray amount, static or dynamic nozzle position including nozzle speed as well as the air atomization pressure and spray time. Thus, a carefully designed siliconization process results in clearly defined, limited silicone levels and reproducible silicone distributions without compromising functionality [7,12,21,25,37].

The objective of the present study was to establish an optimized bake-on siliconization process using a pilot-scale siliconization unit. In particular, we investigated different nozzle positions below the cartridge flange, and variations in spray quantities, pressures and times for pump dosing to control and optimize the spray pattern as well as the silicone distribution and layer thickness along the cartridge barrel. The concentration of the silicone emulsion was clearly defined to yield adequate silicone levels, ensuring adequate extrusion performances of the piston even after long-term storage.

2. Material and methods

2.1. Materials

DC 365 35% Dimethicone NF Emulsion purchased from Dow Corning GmbH (Wiesbaden, Germany) was diluted to 0.06–3.5% (w/w) using highly purified water. Non-siliconized 5 mL cartridges, pistons, serum stoppers and aluminum seals were obtained from F. Hoffmann-La Roche Ltd. (Basel, Switzerland). Elastomeric components were coated with fluoropolymer (Fluorotec®). Talcum (Ph. Eur. grade) was purchased from VWR International GmbH (Darmstadt, Germany).

2.2. Bake-on siliconization process

Experiments in this study were performed using a SVS9061 pilot-scale siliconization unit from Bausch + Ströbel (B + S) Maschinenfabrik Ilshofen GmbH + Co. KG (Ilshofen, Germany). The set-up employed a high precision rotary piston pump with a gliding disk from Saphirwerk AG (Brügg, Switzerland) to deliver silicone emulsion through an external mixing two-fluid nozzle with a swirl inset. A sensor dummy (diameter 0.6 mm) was inserted into the inner concentric tube (diameter 0.8 mm), which resulted in a hollow cone emulsion stream with an annular slit thickness of 0.1 mm (Supporting Information Fig. S1). The delivered amount was manually adjusted by a micrometer screw with nominal settings from 1 to 3 mm in 0.1 mm increments [39]. The screw setting defined the position of the gliding disk, thereby optimizing the gap between the piston and the bottom of the cylinder. Therefore, the micrometer screw allowed the absolute adjustment of dosing volume. A servo automated actuator controlled both static and dynamic nozzle positions while in turn an operator touch screen provided full control of the servo automated actuator settings. For atomization, compressed air was manually controlled by a pressure reducer (0.8–2.5 bar) and automatically monitored on the operator touch screen. Compressed air was adjusted by a gauge valve prior to emulsion dosing. The time for pump dosing was set on the operator touch screen. Up to 18 cartridges were fed manually into the star wheel with flange downwards. Finally, a two-hand circuit was used to safely initiate the spray process.

The cartridges were subsequently treated in a TSQ U03 heat-tunnel from Robert Bosch GmbH (Stuttgart, Germany) at 316 °C for 12 min.

2.3. Gravimetric analysis

After every adjustment of the pump screw or spray parameters, the emulsion spray was initially collected in a 2R vial, which was