Optimization of the bake-on siliconization of cartridges. Part II: Investigations into burn-in time and temperature

Stefanie Funke a, Julia Matilainen b, Heiko Nalenz b, Karoline Bechtold-Peters b, Hanns-Christian Mahler b, Florian Vetter c, Christoph Müller c, Franz Bracher c, Wolfgang Friess a,⇑

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

A R T I C L E   I N F O
Article info
Received 24 February 2016
Revised 13 May 2016
Accepted in revised form 18 May 2016
Available online 17 June 2016

Keywords:
Bake-on siliconization
Cartridge
Heat-tunnel
Siloxanes
FTIR
Functionality
3D-Laser Scanning Microscopy
Silicone layer thickness
Silicone level

A B S T R A C T
Combination products have become popular formats for the delivery of parenteral medications. Bake-on siliconization of glass syringes or cartridges allows good piston break-loose and gliding during injection at low silicone levels. Although widely implemented in industry, still little is known and published on the effect of the bake-on process on the silicone level, layer thickness and chemical composition. In this study, cartridges were bake-on siliconized in a heat-tunnel by varying both temperature from 200 to 350 °C for 12 min and time from 5 min to 3 h at 316 °C. Furthermore, a heat-oven with air-exchange was established as an experimental model. Heat treatment led to a time- and temperature-dependent decrease in the silicone level and layer thickness. After 1 h at 316 °C lubrication was insufficient. The silicone levels substantially decreased between 250 and 316 °C after 12 min. After bake-on, the peak molecular weight of the silicone remained unchanged while fractions below 5000 g/mol were removed at 316 °C. Cyclic low molecular weight siloxanes below 5000 g/mol were volatilized under all conditions. Despite most of the baked-on silicone was solvent-extractable, contact angle analysis indicated a strong binding of a remaining, thin silicone film to the glass surface.

C © 2016 Elsevier B.V. All rights reserved.

1. Introduction

Pre-filled syringes and cartridge-based drug/device combination products have gained wide acceptance in the delivery of parenteral drug products due to several advantages including ease of self-administration, accurate dosing, decreased risk for contamination, and less overfill [1–5].

Silicone oil is used as lubricant allowing the piston to break-loose and glide smoothly within the glass barrel during injection [6–9]. Siliconeization is performed by either spraying-on silicone oil, e.g., Dow Corning 360 Medical Fluid, referred to as spray-on siliconization, or by applying silicone emulsion such as diluted Dow Corning 365 35% Dimethicone NF Emulsion, followed by bake-on at elevated temperature of approximately 300 °C for 10–30 min [10–16]. Bake-on siliconization results in relatively lower silicone levels < 0.1 mg/barrel [17–19] compared to spray-on siliconization with 0.2–1 mg/barrel [8,16,17,20–25]. Alternative siliconization methods include dip coating of Dow Corning 360 Medical Fluid dissolved in solvent [26,27] or applying cross-linkable silicone, such as VDT-731 by plasma-enhanced chemical vapor deposition [28] and Dow Corning MDX4-4159 with subsequent polymerization by ultraviolet irradiation or by curing at elevated temperature [27].

The main advantage of bake-on siliconization is to limit silicone migration into the drug product without compromising functionality [18,20,21,24,26,29,30]. However, based on thermal decomposition during bake-on, it has been argued that the processing window is narrow due to a change in the silicone bulk properties and the potential impact on extrusion forces [21]. Volatilization, depolymerization and thermo-oxidation have been identified as main mechanisms during thermal decomposition of silicone oil. The most commonly used lubricant trimethylsiloxy-endcapped
polydimethylsiloxane (PDMS) [31] decomposes into volatile low molecular weight siloxanes (LMWS), SiO₂, H₂O and CO₂ [32–34]. In parallel, thermo-oxidation may initiate cross-linking via a complex radical mechanism [33]. As both processes overlap to some extent, the change in molecular weight of the polymer is hardly predictable. Thomas et al. found either a negligible change or decrease in molecular weight depending on both thermal depolymerization and rearrangement of siloxane bonds compensating each other in vacuum [34]. Mundry et al. suggested an increase in number and weight average molecular weight (\(M_n\) and \(M_w\)) attributed to the volatilization of a significant portion of LMWS while the peak average molecular weight (\(M_p\)) remained unchanged. Therefore, cross-linking was unlikely to be the main mechanism upon bake-on [10]. Suitable methods to analyze the molecular weight of PDMS are gel permeation chromatography (GPC) followed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry [35,36], evaporative light scattering detection [37,38], inductively coupled plasma atomic emission spectrometry [39] or refractive index detection (RID) [10,40,41].

The application of silicone oil in health care includes using as lubricant [31], for the treatment of retinal detachment and for soft tissue augmentation due to its biological inertness [42]. However, certain LMWS contained as residues from polymer synthesis [43,44] have been assessed for their toxic effect. Cyclic LMWS, i.e., cyclodimethylsiloxanes, are indicated as Dn where D = [(CH₃)₂SiO]. In particular, D4 has been associated with impaired fertility (D4 is labeled reproductive category II, globally harmonized system [45]). Both D4 and D5 were related to potential carcinogenic effects resulting in an increase in uterine tumors, as well as hepatomegaly in rats and mice [46,47]. LMWS are known to migrate into various, preferentially lipid-rich compartments [48], which increases the risk for a wide and persistent distribution throughout the body in mice [49] and human plasma of implant recipients [50]. Other studies suggested D4-induced denaturation and aggregation of fibronectin and fibrinogen [51,52]. Consequently, the thermal decomposition of PDMS into LMWS during bake-on may be of critical toxicological concern.

Most studies mainly investigated the decomposition of silicone bulk samples exposed to artificial heat-treatment rather than using baked-on silicone, solvent-extracted from syringes or cartridges. Therefore, though thermal “fixation” and “chemical binding” of silicone to the glass surface is often postulated [7,13], it is still rarely investigated. After solvent extraction, very thin baked-on silicone layers covalently bound to the glass surface have been found by Mundry et al.; however, most baked-on silicone was still solvent-soluble and therefore a general fixation of the baked-on silicone layer is postulated to be unlikely [12].

Thus, there is currently a substantial gap in understanding and analysis of the thermal decomposition of silicone emulsion upon bake-on. Although bake-on siliconization is an essential step during manufacturing of many parenteral drug products, minimal practical data are available. The purpose of this study was to investigate the impact of different burn-in times and temperatures on the characteristics of the baked-on silicone layer to identify an adequate processing range. Compared to commercial bake-on siliconization processes, 0.6% (w/w) silicone emulsion was sprayed-on using optimized spray parameters followed by bake-on in a heat-tunnel. We propose a toolbox of analytical methods toward full control of the baked-on silicone level, layer thickness distribution and coating functionality. The thermal decomposition of silicone and pharmacologically relevant stabilizers of Dow Corning 365 35% Dimethicone NF Emulsion was characterized with respect to weight loss, cyclic LMWS content and molecular weight distribution of the silicone polymer. The formation of covalent bonds was functionally addressed by contact angle (CA) measurements after removal of the extractable silicone fraction. Finally, the silicone layer characteristics after bake-on in a heat-tunnel were compared with a heat-oven as an experimental model for laboratory-scale experiments.

2. Materials and methods

2.1. Materials

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 (FluroTec®). Microscope glass slides were obtained from VWR International GmbH (Darmstadt, Germany).

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); cyclic LMWS D3, D4, D5, methyl paraben, propyl paraben, tert-butylmethylether and toluene from VWR International GmbH (Darmstadt, Germany); Tween 20 from Croda GmbH (Nettel-Kaldenkirchen, Germany); and cyclic LMWS D6, Triton X-100 from Sigma–Aldrich Chemie GmbH (Taufkirchen, Germany). ReadyCal-Kit polystyrene standards PSS-pskitr-04 were obtained from PSS Polymer Standards Service GmbH (Mainz, Germany).

2.2. 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, two-fluid nozzle. Optimized spray parameters were adapted from previous experiments: a spray quantity of 4 mg, or alternatively of 16 mg silicone emulsion, a fixed nozzle position of 20 mm below the flange, a spray pressure of 1 bar and time for pump dosing of 175 ms [53].

For most experiments, Dow Corning 365 35% Dimethicone NF Emulsion was diluted to 0.6% (w/w) using highly purified water. A higher concentrated silicone emulsion of 3.5% (w/w) was utilized for gas chromatography–mass spectrometry (GC–MS) analysis. For CA experiments, the emulsion was diluted to 1.75% (w/w).

The cartridges were subsequently treated in a TSO U03 heat-tunnel from Robert Bosch GmbH (Stuttgart, Germany). Burn-in temperatures were adjusted from 200 °C to 350 °C at a constant treatment time of 12 min. Varying burn-in times ranging from 5 min to 3 h were studied at a constant temperature of 316 °C.

The bake-on process was further investigated in a heat-oven Heraeus WU6100 from Thermo Scientific Inc. (Waltham, MA, USA) without air-exchange and with air-exchange of 2.5 m³/h. For temperature profile measurements, five cartridges in the center and at each side of a wire basket used as holder during bake-on were equipped with two T-type thermocouples (TC) from GE Sensing & Inspection Technologies GmbH (Hürth, Germany) at the top and bottom of the individual cartridge. TCs were affixed in the cartridge using Kapton 3 M™ tape from Reinhard Krückemeyer GmbH & Co. KG (Wilnsdorf, Germany) to secure the TC firmly against the neck of the cartridge. An additional TC was directly placed into the oven. TCs were calibrated from 180 °C to 360 °C, and verified at 316 °C with a final accuracy of 315.5 °C ± 0.2 °C. At burn-in temperatures ≥ 200 °C a sensitivity of 1 °C is accepted to be sufficient [54].

2.3. Extraction and Fourier transform infrared (FTIR) quantification

The baked-on silicone level was determined by a combination of heptane extraction (900 µL heptane, two rinsing steps à