Silicone Oil Induced Effects in Pharmaceutical Glass Vials

Testing Methods for Visualisation, Identification and Quantification

Uwe Rothhaar, Daniel Haines, Volker Scheumann

SCHOTT AG, Mainz

Correspondence: Dr. Uwe Rothhaar, SCHOTT AG, Hattenbergstr. 10, 55122 Mainz (Germany)

ABSTRACT

Pharmaceutical fillers experience a variety of nuisance problems when packaging formulations into containers such as syringes, cartridges, and vials. For liquid biological or freeze-dried drug formulations, the presence of deliberately applied or adventitiously migrating silicone oil can lead to undesired effects such as beading, spotting, abnormal menisci, particulate formation, aggregation, and adsorption. Determining the root cause for these issues is often challenging as for each of the aforementioned effects there are numerous potential root causes, many of which are not necessarily linked to the presence/absence of silicone. There is a need in the pharmaceutical industry for a straightforward, compact, and robust study protocol for determining if the observed container/solution issues are due to presence/absence/amount of silicone oil.

The authors provide data from pharmaceutical glass vials addressing potential silicone migration and cross-contamination based on qualitative and quantitative characterisation methods. The combination of different methods (wetting testing, ToF-SIMS and GF-AAS) is a powerful tool for a reliable assessment. The simulating test results confirm that a cross-contamination of glass vials through a pharmaceutical washing process and migration of silicone from a preceding processing of baked-on silicone vials is unlikely.

ZUSAMMENFASSUNG

Silikonöl-induzierte Effekte in pharmazeutischen Glasfläschchen: Analytische Methoden zur Visualisierung, Identifizierung und Quantifizierung

Beim Abfüllen von flüssigen oder gefriergetrockneten Medikamenten in Primärpackmittel wie Spritzen, Karpulen und Fläschchen kann eine Vielzahl von Störungen auftreten. Beispielsweise ergeben sich durch absichtlich aufgebrachtes oder zufällig migriertes Silikonöl häufig Probleme wie die Ausbildung von Tropfen oder Flecken, ungewöhnliche Formen der Fülllinie (Menisken), das Auftreten von Partikeln oder Aggregation und Adsorption. Die Ursachenfindung für diese Probleme ist oft herausfordernd, da es für jede der oben genannten Phänomene zahlreiche potenzielle Erklärungen gibt, von denen manche aber nicht unbedingt mit dem Vorhandensein oder dem Fehlen von Silikon zusammenhängen. In der pharmazeutischen Industrie besteht daher ein Bedarf an unkomplizierten, kompakten und robusten Methoden zur Untersuchung von ungewöhnlichen Wechselwirkungen zwischen dem Packmittel und dem Medikament, um eine mögliche Beteiligung von vorhandenem oder fehlendem Silikonöl zu bewerten. Im folgenden Artikel werden qualitative und quantitative Methoden zur Charakterisierung von potenzieller Silikonmigration und Kreuzkontamination auf der Basis exemplarischer Daten für Glasfläschchen vorgestellt. Aus der Kombination verschiedener Methoden (Benetzungstest, ToF-SIMS und GF-AAS) ergibt sich ein leistungsfähiges Werkzeug für eine zuverlässige Bewertung. Die Ergebnisse bestätigen z. B., dass eine Kontamination von Glasfläschchen durch einen pharmazeutischen Waschprozess von einbrenn-silikonisierten Fläschchen unwahrscheinlich ist.

KEY WORDS

- Silicone oil
- cross-contamination
- migration
- droplet test
- ToF-SIMS
- GF-AAS

Pharm. Ind. 84, Nr. 1, 120–127 (2022)

Introduction

Siliconisation of components used for pharmaceutical packaging is a very common treatment to impart a broad range of different properties. Up to now most prefilled syringes and cartridges require silicone oil-based lubrication of the inner glass barrel to achieve a reliable injection force over the shelf life, although first silicone free systems are being introduced to the market. These lubricant layers are usually applied to glass containers using 2 different manufacturing processes, namely baked-on or sprayed-on siliconisation. While silicone oil with high viscosity is directly deposited during the sprayed-on process, an aqueous silicone emulsion with significantly less silicone oil is spread at the inner surface and the glass container subsequently heated to a

temperature in the range of 250–350 °C to provide baked-on silicone layers. As a result, higher amounts of silicone are usually found for the containers with a spray-on siliconisation (several 100 µg up to 1 mg per container) compared to baked-on (several 10 µg up to a few 100 µg per container) [1, 2, 3]. As an undesired side-effect, particles can be observed within drugs being in contact with these siliconised surfaces after storage and agitation. Beside silicone oil droplets, especially protein aggregates or protein-silicone-compounds found in biopharmaceutical drugs are of concern and the subject of many investigations [2, 4]. Among other effects, higher amounts of silicone have been reported to increase the potential to induce such particles.

By using silicone layers at the interior surface of vials the reduction/minimisation of the sticking of various biological molecules could be realised [5]. The hydrophobic behaviour of siliconised vials is utilised to avoid the creeping for lyophilised drug formulations, the so-called, 'fogging effect' or to reduce the residual volume loss when drawing up the filling into a syringe [6, 7]. Here too, the siliconisation is realised by a baked-on process. The amount of silicone needed to ensure these functional properties is significantly lower compared to lubrication layers. It has been shown that even a few micrograms of silicone are sufficient to ensure the hydrophobic behaviour of a 20 ml vial [8].

Silicone oil is also used on stoppers (and tip-caps) to prevent sticking in the feeder bowls used during placement to the primary packaging container. After positioning into the container, excess silicone oil has been shown to migrate from the stopper surface, resulting in potential adverse interaction with the drug formulation [9]. Silicone oil migration from stoppers to interior surfaces of vials can lead to abnormal menisci (flat or inverted) and as a consequence to vial rejection during automated final inspection via camera-based systems and/or low fill sensors.

Various methods have been used to confirm the presence/absence and/or various attributes of silicone oil on primary pharmaceutical packaging components. Surface energy determination methods include contact angle [6] and the use of inks with known surface tension [7]. Coating uniformity methods include talcum, Fourier-transform infrared spectroscopy (FTIR), 3D laser scanning microscopy [1], glass dust, reflectometry, and machine vision for observation of striae effects [10]. Chemical identification methods include FTIR, Nuclear Magnetic Resonance (NMR), Graphite Furnace Atomic Absorption Spectrometry (GF-AAS) [8] or Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) [7]. Quantification of deposited amounts include FTIR [1] determination of silicone oil interaction with drug formulation components resulting in various sized particles, which have been assessed in [3] by mass flow imaging, turbidity, resonant mass measurements, dynamic light scattering, and light obscuration, while imaging flow cytometry was used in [4].

Testing laboratories are often tasked with the rapid identification and root cause verification for various pharmaceutical vial filling/storage problems experienced by pharmaceutical fillers for beading, fogging, abnormal menisci, spotting, etc. The number of samples is sometimes extremely limited. In this article, the authors provide data to answer 4 common vial questions related to the presence/absence of silicone oil:

1. can silicone oil migrate/be removed from a siliconised vial surface by water during vial washing,
2. can unsiliconised vial surfaces become contaminated with adventitious silicone oil,
3. does depyrogenation change the surface energy (i.e., hydrophobicity) of a vial with adventitiously deposited silicone oil, and
4. what methodology is suitable to extract and quantitatively determine the amount of silicone oil present on a vial surface without suffering loss of silicone oil to preparatory equipment?

The answers to these questions will aid pharmaceutical fillers in understanding how to troubleshoot and determine root cause yes/no for silicone oil. First, to assess the propensity of silicone displacement from siliconised vials filled with water, extracts generated under pronounced shaking stress and prolonged storage at 60 °C were transferred to non-siliconised vials. A droplet test based on the spreading of water droplets and adapted to the geometry of the vials was used as a first test to directly visualise any changes of the hydrophobicity of the surfaces. Second, the ability for low levels of spiked-in silicone to modify the wetting behaviour of glass vials was demonstrated via the droplet test with the confirmation of the root cause for alteration of the surface properties characterised by applying ToF-SIMS, which is a sensitive method to identify presence/absence of silicone molecules [7, 11,12]. Third, adventitiously deposited silicone oil was shown to survive depyrogenation conditions with the retainment of surface hydrophobicity as verified by the droplet test. Fourth, commercially available siliconised vials were extracted with organic solvent and directly transferred to the injection port of a GF-AAS without loss of analyte to ancillary preparatory equipment, and the amount of extractable silicone oil per container was quantified.

Materials and Methods

Materials

The study was performed with 2 sets of 10 ml tubular vials made of clear borosilicate glass (FIOLAX®, a glass with a thermal coefficient of expansion of 5.1 x 10^{-6} per K). One set consisted of commercially available siliconised vials was produced by a baked-on process, while the second set was comprised of non-siliconised vials. First, all vials were cleaned in 2 steps: (1) filled and emptied 3 times with tap water and (2) filled and emptied 3 times with purified water. The purified water was

generated by a purification system from Sartorius with a conductivity below 0.06 µS/cm at 25 °C and a total organic content (TOC) below 5 ppb. This water quality was used for the last cleaning step as well as for the filling of the vials with a volume of 10 ml by a pipette. For the spiking experiments DuPont Liveo™ 360 silicone oil was added to water to achieve a 1:10,000 mixture.

The filled vials were covered with aluminium foil and incubated for 2 hrs at 60 °C while shaking at 100 rpm with the incubation shaker KS 4000 from IKA. After emptying, some of the vials additionally went through a depyrogenation process at 330 °C for 30 min. This was accomplished by using a batch oven from the company Despatch which is equipped with a forced cooling unit and a HEPA filter system.

To get access to the interior surface, the vials were scribed and broken into 2 halves avoiding contaminations from more commonly used cutting or sawing processes, which should not be applied for sample preparation in this case. One half was used for the droplet test while the second half was retained for a potential analysis with TOF-SIMS.

Methods

The wetting behaviour (surface wetting homogeneity) of the vials was determined with an in-house developed droplet test visualising the spreading of coloured water droplets. By using a computer controlled XYZ-stage with a syringe dispensing unit, a number of coloured water droplets with a volume of 2 µl each can be positioned in a line from the shoulder to the wall near bottom area of the vial. The coloration of the water is achieved by adding a small amount of methylene blue. This qualitative test allows an assessment of the hydrophobicity especially in direct comparison to reference vials with known wetting behaviour (e.g., siliconized vials).

TOF-SIMS measurements were performed with a TOF-SIMS IV-100 instrument from ION-TOF. The spectra were acquired under a 15 keV Gallium ion (Ga+) bombardment of sample pieces from the interior vial surface. Only the positive secondary ions signals were analysed (positive mode) to identify a potential coverage with silicone. Charge compensation was achieved by applying low-energy electrons from a flood gun.

The amount of silicone that could be extracted from the siliconised vials was determined by applying an ultrasonication extraction of vials filled to the brimful capacity with n-heptane for 30 min (LiChrosolv® for liquid chromatography). In a second step, the organically soluble silicon (Si) within this extract was analysed with graphite furnace – atomic absorption spectrometry GF-AAS (model ContrAA 700) and reported as polydimethylsiloxane (PDMS) with a Si-content of 38 wt.-%.

Results

Determination of extent of silicone displacement from siliconized vials during washing

Baked-on silicone layers are used to tailor the surface properties of vials. Applied at the interior a hydrophobic surface is created which can help to completely empty the vial or to achieve a more compact lyophilised drug product. In other cases, the exterior surface is coated with silicone to reduce the friction and abrasion, especially in direct glass to glass contact occurring during the pharmaceutical vial filling process. The silicone layer withstands a depyrogenation step and is not seen to influence the results of the optical inspection because of its chemical and optical properties.

Nevertheless, a displacement of silicone from the interior to the exterior surface seems possible or vice versa, especially during the washing process. To get a first impression about the likeliness of such an effect, a worst-case experiment was conducted. Siliconised vials were filled with 10 ml of purified water, capped with aluminium foil and incubated for 2 hrs at a temperature of 60 °C while shaking at 100 rpm. In a next step, an aliquot of 5 ml of the extract from each vial was transferred one to one in washed non-siliconised vials and filled up with purified water to achieve 10 ml again. These vials filled with in a 1:1 dilution of the extract, were again incubated for 2 hrs at a temperature of 60 °C. To assess the impact of a potential silicone displacement on the surface properties of the non-siliconised vials the wetting behaviour of the interior vial surface can be characterised by the droplet test. This is a highly sensitive method to prove even small amounts of silicone on a glass surface.

In Fig. 1 the results of the droplet test are visualised for

a) siliconised vials,
b) non-siliconised vials, and
c) non-siliconised vials after incubation with the 1:1 dilution of the extract.

4 single droplets were placed in a row from the shoulder down to the wall near bottom area. For the siliconised vials all the droplets exhibited a clearly defined spherical shape, indicating a hydrophobic surface. In contrast an extensive spreading of the coloured water was observed for the non-siliconised vials as the droplets merged into each other. This hydrophilic behaviour correlating with small contact angles for water is expected for a clean glass surface having a high surface energy. Similar observations for siliconised and non-siliconised pharmaceutical containers made of glass are reported elsewhere [13, 14]. The droplet test results of the non-siliconised vials after incubation appear very similar to the results derived for non-siliconised vials without incubation. A comparable spreading of the droplets over the entire vial body interior surface was observed. This means that the wetting behaviour of the vials was not negatively influenced by the incubation cycle including all the handling steps.

Determination of silicone adsorption to non-siliconised vial surface

The results described in the previous section could mean that there is no significant release of silicone during the incubation or that silicone that is released into purified water will not adhere to the surface of the non-siliconised vials and, as a consequence, not modify the wetting behaviour. To get an impression about the impact of a highly diluted silicone/water emulsion onto the surface properties, non-siliconised vials were filled with 10 ml of purified water and in addition, 1 µl of silicone oil was spiked-in to achieve a 1:10,000 mixture. After the incubation (2 hrs at 60 °C with shaking) the vials were emptied and divided in 2 groups. The interior surface of

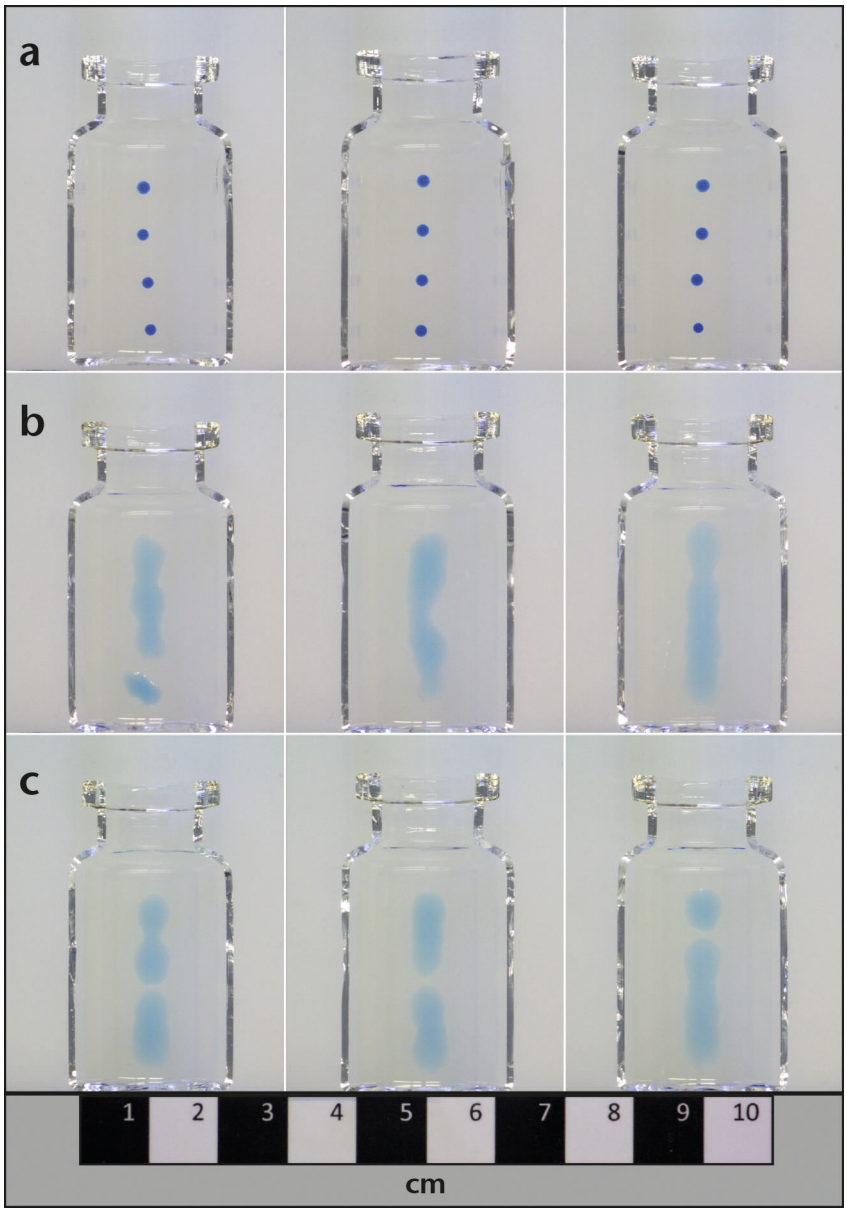

Figure 1: Wetting behaviour of coloured water droplets for a) siliconised vials, b) non-siliconised vials and c) non-siliconised vials after incubation the 1:1 dilution of the extract (source of all figures: the authors).

the first group was directly characterised with the droplet test, while the second group went through a depyogenation process at 330 °C for 30 min before the droplet test was applied.

The appearance of the droplets for 3 representative vials out of each group is depicted in Fig. 2 for
d) spiked vials after incubation, and
e) spiked vials after incubation and depyrogenation.
In both cases the droplets did not spread significantly. They are clearly separated from each other, which is characteristic for a more hydrophobic surface. Within a single vial, no difference can be observed between the shoulder area, mid-body, or wall near bottom. In tendency, the droplets at the surface of the depyrogenated vials (e) appear smaller and more spherical indicating somewhat higher contact angles. These experimental results suggest that during the incubation sufficient silicone from the highly diluted emulsion adhered at the interior surface causing the observed hydrophobic effect. Furthermore, this change in the wetting behaviour could not be removed by heat-treatment up to 330 °C during depyogenation.

ToF-SIMS spectra were acquired from the interior surface of vials directly after the incubation (d) to verify the assumption of a silicone coverage. A representative spectrum in the mass range up to m/z = 300 taken from the wall near shoulder area is depicted in Fig. 3. A number of peaks, which represent the characteristic fragmentation pattern of silicone-like substances were found at m/z values (whole-numbered): 43, 73, 117, 147, 207, 221 and 281. The chemical structure of the corresponding fragments is listed in Table 1 as also described elsewhere [8, 11, 12]. The related peaks are marked with red dots in Fig. 3. In addition, pronounced mass peaks from glass components at nominal masses of 23 (Na^+), 27 (Al^+), 28 (Si^+) and 40 (Ca^+) are observed.

Table 2 compares the ToF-SIMS ion signal intensities (peak heights) for the silicone fragments at m/z values (whole-numbered): 73 ($SiC_3H_9^+$), 117 ($Si_2C_3H_9O^+$), 147 ($Si_2C_5H_{15}O^+$) and 207 ($Si_3C_5H_{15}O_3^+$) for a spiked vial after incubation to those from the interior surface of a siliconised vial. The signal heights range from a few hundred to nearly ten thousand for the incubated vial. The single peaks were well defined without significant mass interferences and very clear above the background level. Within small variations the intensities derived for the siliconised vial are about 11 times higher for all 4 fragments. Independent of the method used to deposit silicone oil to these vials (baked-on siliconisation for the commercially available vials, liquid deposition from a spiked solution), the fragmentation pattern observed via ToF-SIMS analysis is the same.

Pharm. Ind. 84, Nr. 1, 120–127 (2022)

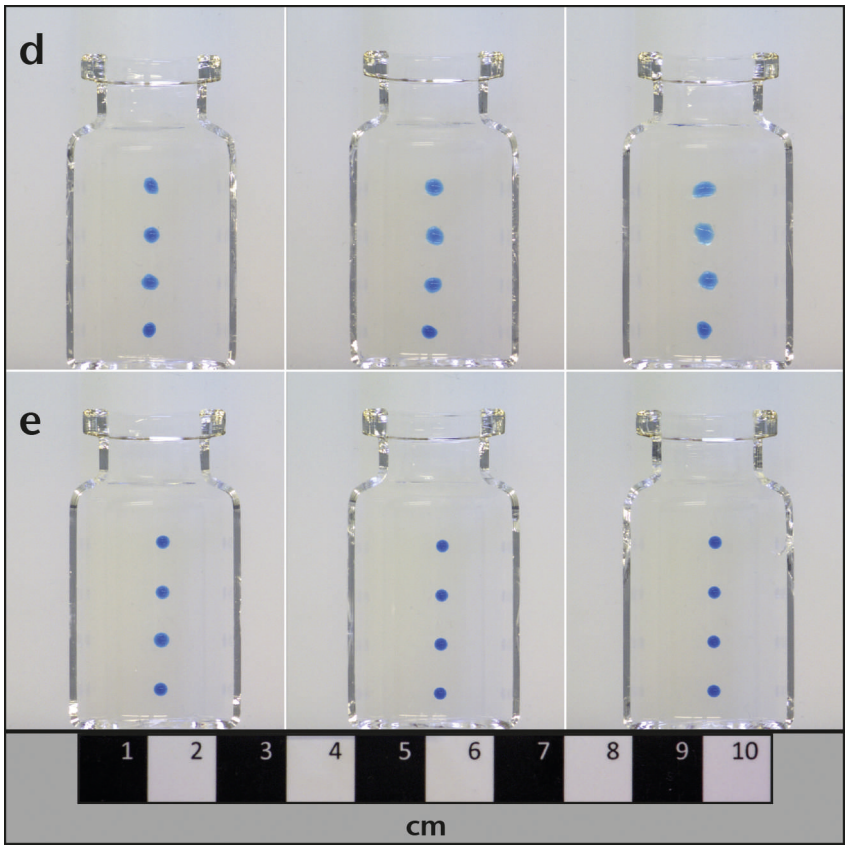

Figure 2: Wetting behaviour of coloured water droplets for d) spiked vials after incubation and e) spiked vials after incubation and depyrogenation.

in different conditions. To get an information about the amount of silicone that is present in a given container, an ultrasonic extraction over a time period of 30 min for 3 siliconised vials filled with n-heptane was performed. The extract was directly analysed with GF-AAS and the amount of silicone was calculated on the basis of the determined Si-concentration. This procedure does not require additional surrounding containers as are usually used for reflux or soxhlet extractions and minimises the risk of losing silicone due to adsorption in that extraction apparatus. Within the measurement uncertainty the same silicone amount of about 30 µg silicone was found for each of the vials (see Table 3). Based on the geometric conditions of the 10 ml vials with an inner diameter of 2.2 cm and a filling height of about 3.6 cm, the extracted area resulted in 28.7 cm^2. Considering a mass density of 0.97 g/cm^3 for silicone, the 30 µg per vial corresponds to a layer thickness of about 11 nm.

Table 1

Characteristic silicone fragments that can be found in positive ToF-SIMS spectra of siliconised surfaces.

m/z [amu] (whole-numbered)	Silicone fragment
43	$SiCH_3^+$
73	$SiC_3H_9^+$
117	$Si_2C_3H_9O^+$
147	$Si_2C_5H_{15}O^+$
207	$Si_3C_5H_{15}O_3^+$
221	$Si_3C_7H_{21}O_2^+$
281	$Si_4C_7H_{21}O_4^+$

Method for the determination of the amount of extractable silicone oil

The aforementioned experimental results are focused on the wetting behaviour and the identification of the chemical structure of the interior surface of vials

After the extraction with n-heptane the vials were rinsed with purified water. Subsequently, the interior surface was characterised with the droplet test. As depicted in Fig. 4 the droplets did not spread, they appear spherical without a significant variation within a vial or from vial to vial, very similar to siliconised vials before the extraction (Fig. 1a). ToF-SIMS analysis from the corresponding second half of one of the vials revealed the presence of silicone-like material via the characteristic peaks that fit to the fragmentation pattern listed in Table 1. Obviously, some silicone remained at the surface that could not be released/extracted with the n-heptane.

This observation fits to published data [10, 15] verifying that strong covalent bonds are formed between the glass surface and the Polydimethylsiloxane (PDMS) chains This results in a thin hydrophobic coating bonded to the glass in a way that it cannot be removed by organic solvents. Expecting that these PDMS chains in direct contact with the glass are more or less lying on the surface [15], a kind of a monolayer with a thickness equal to the chain thickness of about 0.8 nm can be assumed [8].

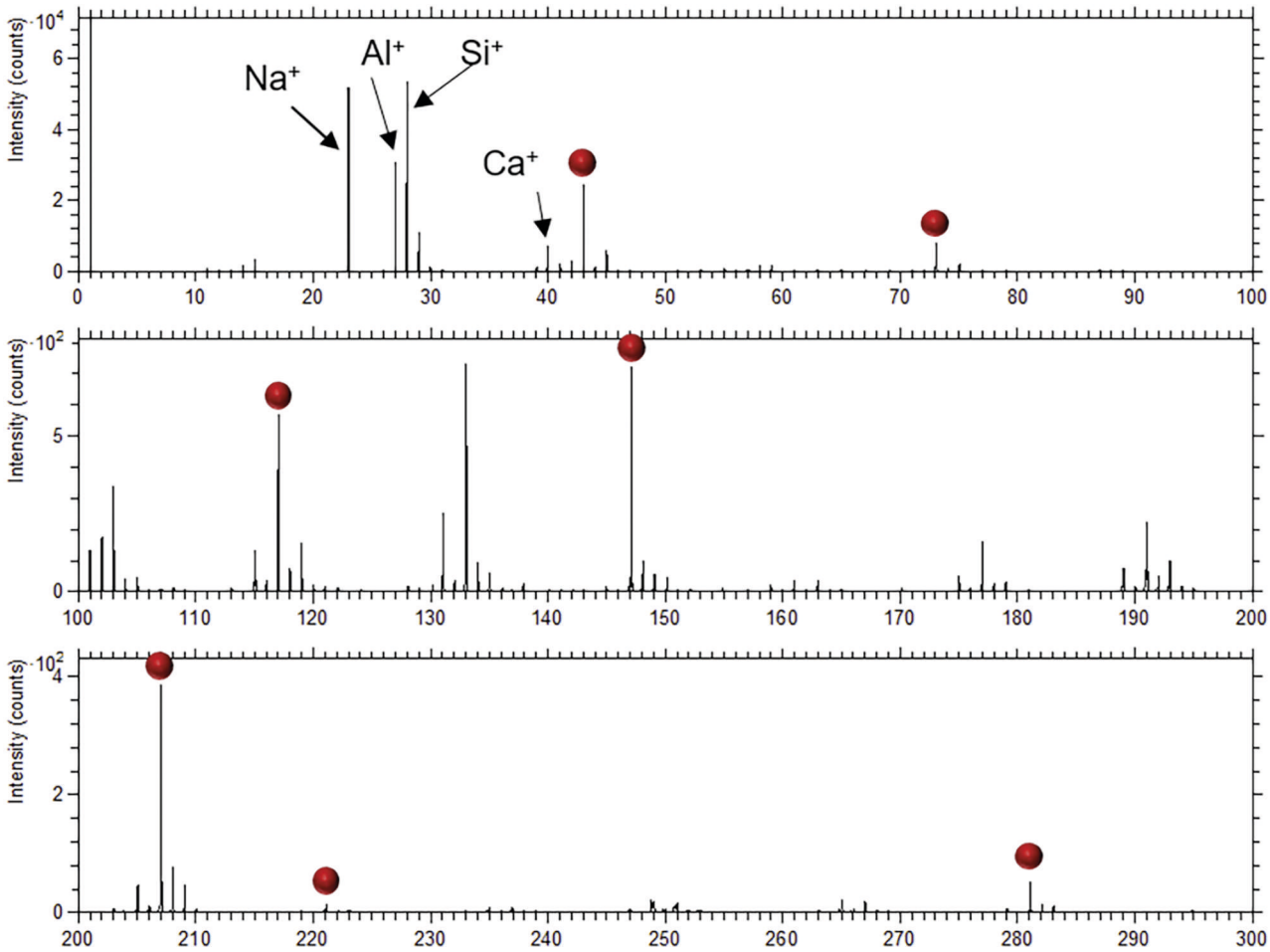

Figure 3: Positive ToF-SIMS spectrum of d) spiked vials after incubation (wall near shoulder area); red dots mark characteristic silicone fragments (see Table 1).

Table 2

The signal intensities found for different silicone fragments for a siliconised vial and a spiked vial after incubation.

m/z [amu] (whole-numbered)	Siliconised vial [counts]	Vial after incubation [counts]	Ratio of intensities Siliconised/Incubated
73	1×10^5	9×10^3	11.1
117	7×10^3	6×10^2	11.7
147	1×10^4	8×10^2	12.5
207	4×10^3	4×10^2	10.0

Discussion

Silicone oil migration from component to component (stopper to container surface), component to solution, and solution to component (container surface) continues to be a source of concern for pharmaceutical fillers due to the alteration of the container surface properties. Applying washing water from a simulated excessive vial washing of a siliconised vial surface to a non-siliconised vial did not show any change in the hydrophilic wetting behaviour as verified using qualitative droplet testing. This result indicates that the vial washing process for commercially baked-on siliconized vials would not be the most likely source of silicone oil cross-contamination of a vial surface for pharmaceutical fillers. To avoid any misunderstandings, it is necessary to mention that our simulated washing experiment did not give any information about the propensity of adsorption, silicone oil droplet formation or silicone induced particle generation while drugs are stored in siliconised containers.

Subsequent testing of 1:10,000 spiked silicone oil into non-siliconised vials confirmed that silicone oil transfer/migration from the solution to the vial surface, and that

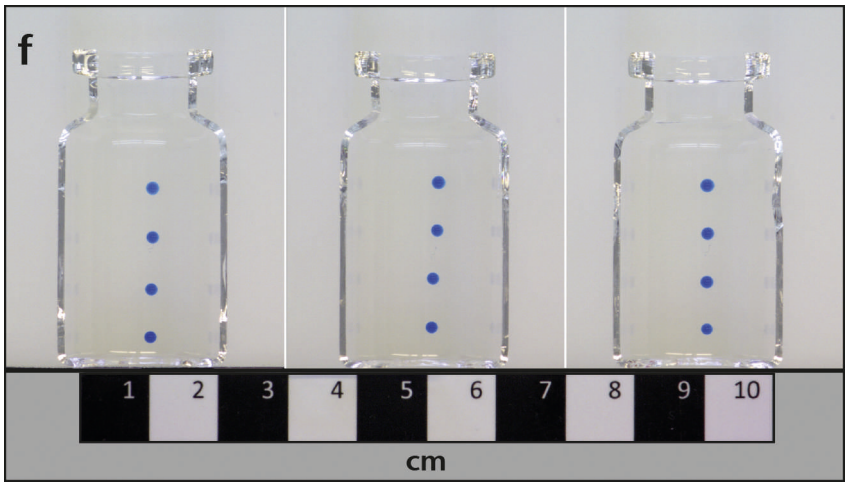

Figure 4: Wetting behaviour of coloured water droplets for f) siliconised vials after extraction with n-heptane.

Table 3

Amount of totally extractable silicone for 3 single siliconised vials (LoQ: 4.0 µg/vial).

Extractable silicone Vial 1 [µg/vial]	Extractable silicone Vial 2 [µg/vial]	Extractable silicone Vial 3 [µg/vial]
30 ± 20 %	28 ± 20 %	30 ± 20 %

subsequent depyrogenation conditions were not sufficient to remove the deposited silicone oil from the surface. This was verified by qualitative droplet measurements and ToF-SIMS yes/no determination of silicone oil on the glass vial surface. This confirms that if silicone oil is introduced inadvertently to a non-siliconised glass vial prior to filling, a change of the surface energy is expected, which can subsequently manifest itself through undesired events such as beading, abnormal menisci, adsorption, etc. This result also supports a possible root cause mode whereby silicone oil may be found on the interior vial surface after filling due to silicone oil migration from the stopper after filling.

Quantitative determination for the amount of silicone oil present in deliberately siliconised vials was demonstrated by ultrasonic extraction with n-heptane and analysis via GF-AAS resulting in silicone amounts of about 30 µg per 10 ml vial. The authors confirmed residual silicone oil at the surface after the extraction by the organic solvent by hydrophobic wetting behaviour and ToF-SIMS measurements. This finding is most probably correlated to a first silicone (mono)-layer tightly bound to the glass surface.

REFERENCES

[1] Funke S, Matilainen J, Nalenz H, Bechtold-Peters K, Mahler H-C, Friess W. Optimization of the bake-on siliconisation of cartridges. Part I: Optimization of the spray-on parameters. Eur J Pharm Biopharm. 2016;104:200–215

[2] Bee JS, Frey VV, Javed U, Chung J, Corcoran ML, Roussel PS, Krause SO, Cash PW, Bishop SM and Dimitrova MN. Characterization of the initial level and migration of silicone oil lubricant in empty prefilled syringes for biologics using infrared spectroscopy. PDA J Pharm Sci Technol. 68 2014;68:494–503.

[3] Funke S, Matilainen J, Nalenz H, Bechtold-Peters K, Mahler H-C, Friess W. Silicone migration from baked-on silicone layers. Particle characterization in placebo and protein solutions. J Pharm Sci. 2016;105:3520–3531

[4] Probst C. Characterization of protein aggregates, silicone oil droplets, and protein-silicone interactions using imaging flow cytometry. J Pharm Sci. 2020;109:364–374

[5] Carl SM, Lindley, DJ, Knipp GT, Morris KR, Oliver E, Becker GW, Arnold RD. Biotechnology-derived drug product development. Gad, Shayne Cox ed. Pharmaceutical Manufacturing Handbook Production and Processes, Wiley-Interscience, 2008,19

[6] Huang M, Childs E, Roffi K, Karim F, Juneau J, Bhatnagar B and Tchessalov S, Investigation of Fogging Behavior in a Lyophilized Drug Product J. Pharm. Sci. 2019;108:1101–1109.

[7] Abdul-Fattah AM, Oeschger R, Roehl H, Bauer Dauphin I, Worgull M, Kallmeyer G, Mahler H-C. Investigating factors leading to fogging of glass vials in lyophilized drug products. Eur J Pharm Biopharm. 2013;85:314–326.

[8] Mundry T., Einbrennsilikonisierung bei pharmazeutischen Glaspackmitteln – Analytische Studien eines Produktionsprozesses. Dissertation, Humboldt-Universität Berlin, 1999

[9] Sacha GA, Saffell-Clemmer W, Abram M, Akers MJ. Practical fundamentals of glass, rubber, and plastic sterile packaging systems. Pharm Dev Technol. 2010;15(1):6–34

[10] Reuter B, Petersen C. Syringe siliconisation trends, methods, analysis procedures. TechnoPharm. 2021;4:238–244

[11] Hale SP, Kappen P, Prissanaroon W, Brack N, Pigram PJ, Liesegang J. Minimizing silicone transfer during micro-contact printing. Appl Surf Sci. 2007;253:3746–3750

[12] Brack N, Rider AN, Halstead B, Pigram PJ. Surface modification of boron fibres for improved strength in composite materials. J Adhesion Sci Technol. 2005;19:857–877

[13] Ditter D, Mahler H-C, Roehl H, Wahl M, Huwyler J, Nieto A, Allmendinger A. Characterization of surface properties of glass vials used as primary packaging material for parenterals. Eur J Pharm Biopharm. 2018;125:58–67

[14] Lorenz B, Rodriguez N, Mangiagalli P, Persson BNJ. Role of hydrophobicity on interfacial fluid flow: Theory and some applications. Eur Phys J. E2014:37–57

[15] Teisala H, Baumli P, Weber SAL, Vollmer D, Butt H-J. Grafting silicone at room temperature – a transparent, scratch resistant nonstick molecular coating. Langmuir 2020;36:4416A4431

Editor-in-Chief: Claudius Arndt. Managing Secretary's office: Valentina Krinizki. Publisher: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Baendelstockweg 20, 88326 Aulendorf (Germany). Phone: +49 (0) 75 25 940 0, Fax: +49 (0) 75 25 940 127. e-mail: redaktion@ecv.de. www.ecv.de. Typesetting: rdz GmbH