Optimizing the Inner Surface of Primary Packaging

Siliconization versus PICVD. What is the difference?

Prof. Dr. Volker Rupertus, Dr. Bernhard Hladik, Diana Löber

SCHOTT Pharmaceutical Systems, Mainz

Abstract

The most important property for a parenteral packaging glass container is the grade of chemical inertness: for the whole period of the predicted shelf life of a specific drug product, the interaction/solution of container-components into the pharma product shall be minimized respectively completely avoided. This behavior was investigated for uncoated glass containers, for those with baked-on silicone coating as well as for an inorganic SiO_2-coating on the inner container surface to prevent direct interaction with the filled drug product. Due to the nature of the applied coating technology a pronounced difference in uniformity and homogeneity of the layer between spray coated and gas phase coated (plasma impulse chemical vapor deposition, PICVD) thin films becomes evident. In opposition to spray coating, the inorganic SiO_2-coating performs with hermetic surface protection with consequently extreme low leaching of glass elements. This ensures especially for highly sensitive biologics the stability of the drug over the shelf life due to the avoidance of interaction with leached ions and a respective pH-shift.

Zusammenfassung

Optimierung der Innenoberflächen von Primärpackmitteln

Die wichtigste Eigenschaft eines parenteralen Primärpackmittels ist der Grad der chemischen Inertheit: Während der Lagerung eines bestimmten Arzneimittels ist die Wechselwirkung von Behälterkomponenten mit dem Pharmaprodukt zu minimieren bzw. vollständig zu vermeiden. Dieses Verhalten wurde sowohl für unbeschichtete Glasbehälter, für solche mit eingebrannter Silikonbeschichtung als auch für eine anorganische SiO_2-Beschichtung auf der inneren Behälteroberfläche untersucht, die eine direkte Wechselwirkung mit dem gefüllten Arzneimittel verhindern sollen. Die angewandte Beschichtungstechnologie bedingt einen erheblichen Unterschied in der Gleichmäßigkeit und Homogenität der Schicht zwischen sprühbeschichteten und mit Gasphasen (plasma impulse chemical vapor deposition, PICVD) beschichteten Dünnfilmen. Im Gegensatz zur Sprühbeschichtung bietet die anorganische SiO_2-Beschichtung einen hermetischen Oberflächenschutz, der extrem niedrige Konzentrationen gelöster Glaselemente (leachables) gewährleistet. Insbesondere für hochempfindliche Biologika ist somit die Stabilität des Arzneimittels über die gesamte Lagerung sichergestellt, da die Wechselwirkung mit ausgelaugten Ionen und eine pH-Verschiebung durch Ionenaustausch verhindert werden.

Introduction

The trend to focus more and more on biomolecule-based parenterals for drug development opens automatically a far more complex field of interaction processes with the primary packaging container during drug shelf life. Adhesion processes on nanoscale at the inner container surface causing denaturation of the respective molecules as well as dis-

Pharm. Ind. 82, Nr. 9, 1192–1198 (2020)

solved glass elements in the buffer solution lead to a variety of complex interaction processes, also depending on the individual glass compositions available in the market.

Type I borosilicate glass, which has been used for decades for nearly all application fields of parenteral pharmaceuticals, has become the gold standard for primary packaging due to its high chemical durability and covering all the demands of regulatory bodies worldwide for parenteral drugs. The amount of leached out ions which might interact with the drug/formulation is typically controlled lot wise according the hydrolytic surface resistance testing including the respective limit values described in e.g. USP <660>, EP 3.2.1 or ISO 4802. Moreover, the ICH-guidelines e.g. Q3D with the given limits for all relevant chemical elements are also typical requirements to be fulfilled by the respective container material.

As those recommendations are the basis for applicable containers, the individual stability testing procedure for a given drug/formulation will ensure drug stability during shelf life and at the time of administration to the patient.

However, the growing emergence of biologics as hormones, enzymes, drugs to treat hemophilia and especially antibodies requires further optimization of the primary container properties to cope with the special needs of those large and complex molecules.

To target appropriate container functionalities the optimization of tubular primary packaging can be achieved by a twofold approach:

The first is a state-of-the-art container manufacturing process with 100 % controls and respective feedback loops to verify a stable processing including the use of a perfect glass tubing as base material (e.g. FIOLAX® CHR (with controlled hydrolytic resistance)) to realize high uniform chemical robustness against the corrosive attack of the pharmaceutical drug product. Ideally, the inner surface also undergoes a chemical inspection lot by lot based on accelerated chemical attack to ensure a minimal variation of the individual container properties over the addressed shelf life for the finished product. This can be achieved via a designed corrosive attack testing based on autoclaving as it is described elsewhere [1–4]. The resulting containers feature a homogenous inner surface property and represent the high end of borosilicate glass packaging.

To improve the chemical properties of typical glass compositions for special applications further, the manifold potential binding partners on atomic scale have to be reduced. A typical practice is the modification of the inner surface of the containers either by e.g. sprayed-on or baked-on silicone films or by physical/chemical hermetic coating procedures e.g. plasma impulse chemical vapor deposited coatings [5,6].

Inner Surface Modifications

Especially for syringes or cartridges with moving rubber materials during intended use, silicone film application is accepted to allow a smooth plunger motion when administered with lower injection forces.

This means the origin of the requirement was mainly of mechanical nature and was not intended to minimize the interaction of inner surface of the container with the drug/formulation. An additional advantage is the improvement of residual emptying, due to the hydrophobic behavior of the siliconized container surface.

■ Silicone Risks & Challenges

Nowadays the majority of siliconized containers are lubricated either by sprayed-on or baked-on technology [7]. T. Mundry et al. [8] reported about a different behavior of silicone layer areas when heat is applied. Only a very thin bonded layer in the low nm-range is formed based on hydroxyl groups available on the glass surface. Those bonds are supposed to be covalent and to be formed during a heat treatment above 300 °C for 10–30 min. This layer is extremely stable up to 400 °C but not homogenously distributed over the glass inner surface [9]. The upper part of the silicone layer with thicknesses of some tenth to more than 100 nm is not entirely fixed by the baked-on process and can be removed by suitable solvents. This fraction is therefore still interacting with the drug product during storage and leading to a dissolution of this silicone layer part into the wet solution [9]. Those effects are additionally reported in various publications resulting in interaction mechanisms of residual free silicone with the therapeutic protein, also causing protein aggregation and/or loss of soluble protein [10–14]. Due to the complex design and nature of proteins, a general prediction of the individual behavior with silicone cannot be made. In some cases, the free silicone species tend to form small silicone droplets, which are often detected as particle contamination of the wet drug product during final inspection [7,15].

Although the pharmaceutical industry is further controversially discussing if the silicone layer acts as a barrier reducing the risk of glass delamination or the amount of leached out ions, this paper is focused on the leachable behavior of pre-treated coated container surfaces.

■ Experimental

To compare the properties of baked-on silicone spray coating with those of chemical vapor deposited SiO_2-coating the following experimental protocol was performed:

Primary packaging containers based on type I borosilicate glass FIOLAX® clear tubing were produced by a standard converting process [16]. All containers were cleaned by a commercial pharmaceutical washing process based on

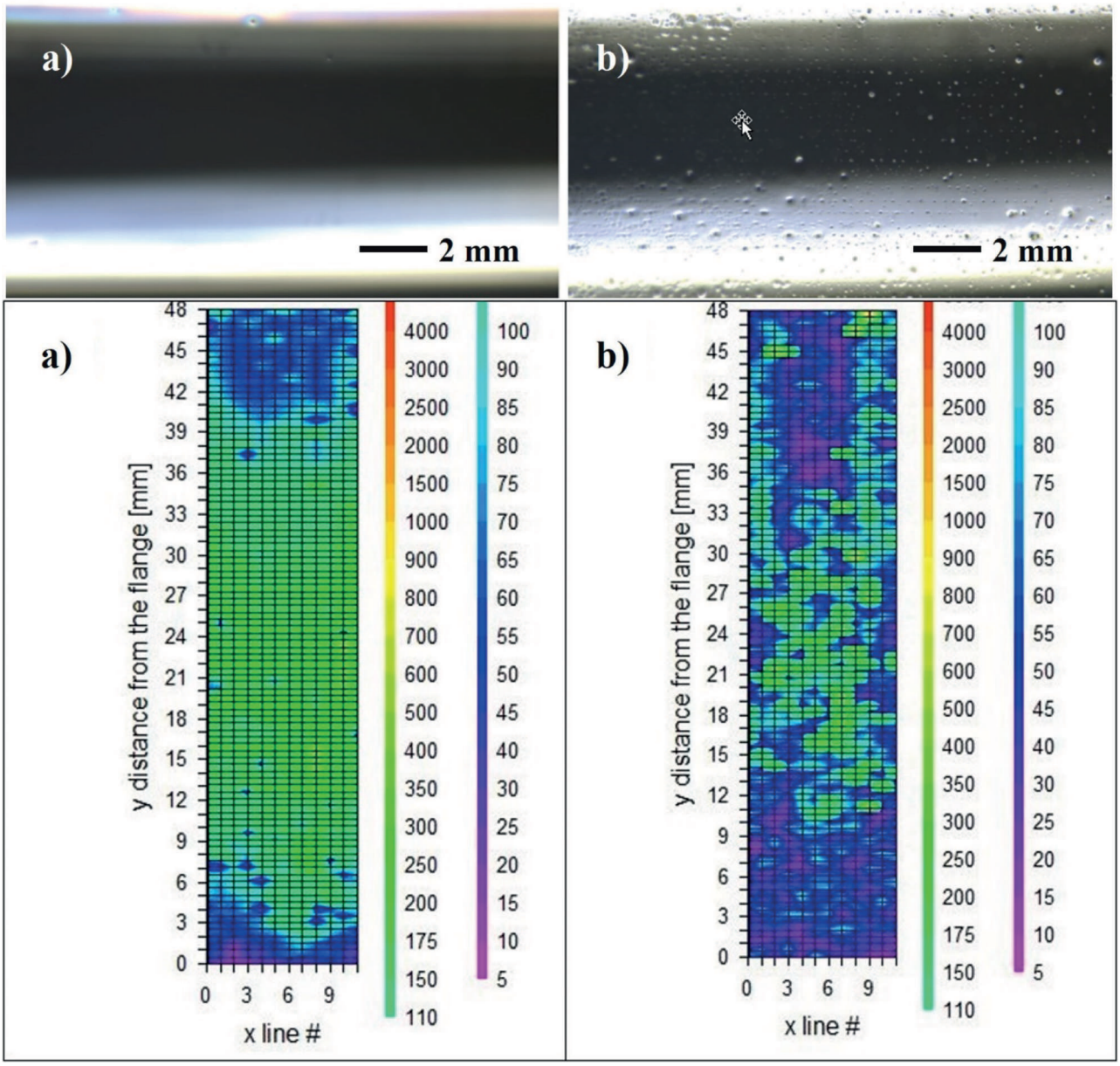


Figure 1: Body of baked-on silicone coated containers. a) before and b) after terminal sterilization processing applying saturated water at 121 °C for 30 min. Top: stereomicroscope images. Bottom: optical reflectometry measurements (x line represents the circumference position: 1 ≙ 30° … 10 ≙ 360°, Source of all figures: SCHOTT).

purified water as last washing step, followed by heat drying to remove residual water.

For baked-on silicone coating, a spray process with a diving nozzle system was applied using a 2 % dilution based on silicone product Dow Corning® 365/366 35 % Dimethicone NF emulsion. The applied silicone spray coating was baked on the inner surface via a thermal heating process step with maximum temperatures up to 300 °C.

The inorganic SiO_2-coating was applied by a chemical vapor deposition technique (PICVD) based on a microwave induced plasma with hexamethyldisiloxane (HMDSO) as precursor gas in combination with oxygen as a reactive partner to deposit stoichiometric SiO_2 thin films.

The characterization of the coating properties was done via optical/visual and wet chemical methods:

- The film homogeneity was qualified by means of an optical measurement system (rap.ID layer explorer, model 9703) using white light and laser reflectometry to determine lateral layer thicknesses from the resulting interference pattern. The surface characterization was done by an optical stereomicroscope (Euromex NexiusZoom), the detailed analysis by a scanning electron microscope (Zeiss Gemini SEM).
- Wet chemistry analyses were performed in the accredited labora-

Pharm. Ind. 82, Nr. 9, 1192–1198 (2020)

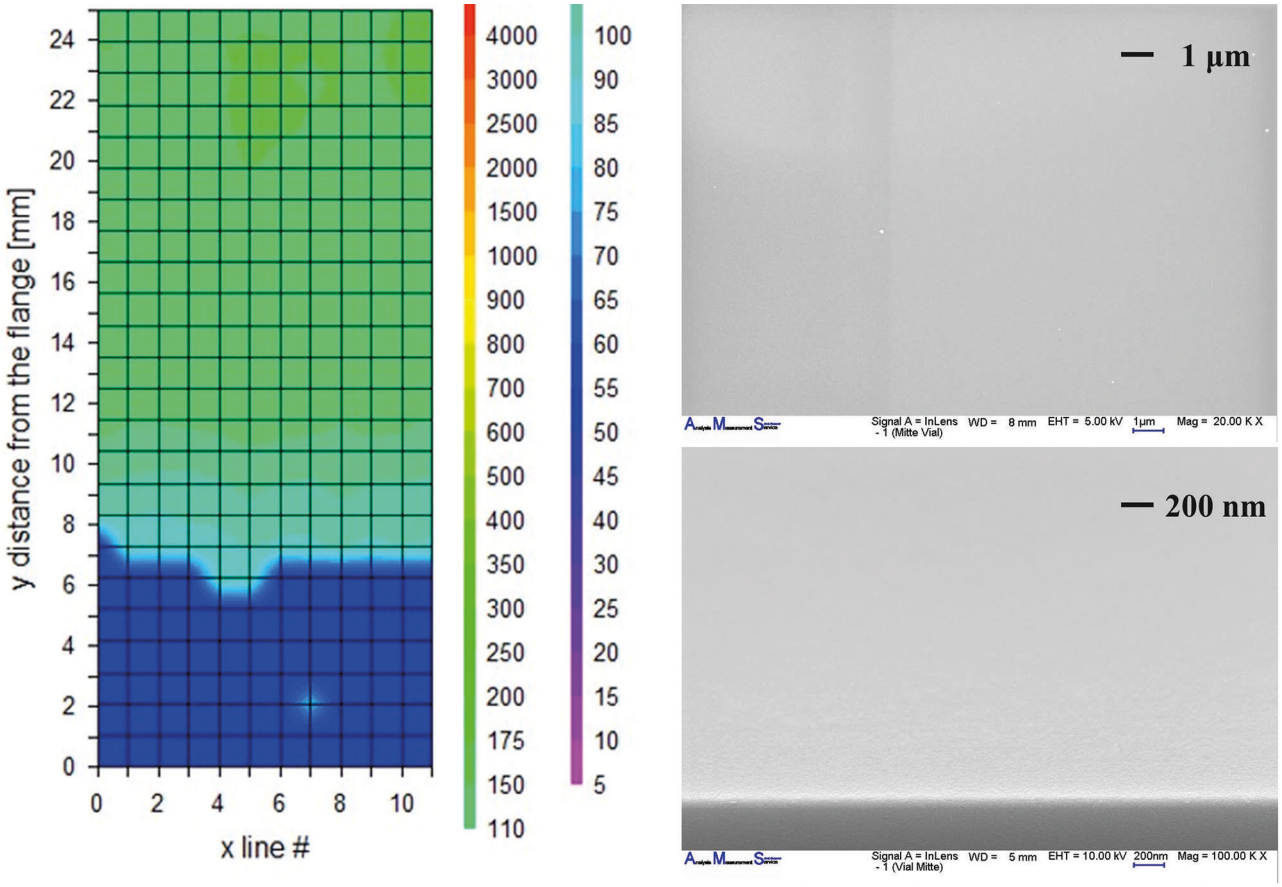


Figure 2: PICVD-coated inner surface of a container. Left: optical reflectometry measurements (x line represents the circumference position: 1 ≙ 30° ...10 ≙ 360°). Right: SEM-image in high resolution, including cross section.

tories of Schott pharma services by means of testing protocols according the international pharmacopeias (<USP> 660; Pharm. Eur. 3.2.1) or ISO 4802-2 for hydrolytic resistance of the interior surfaces of glass containers and ICH/Q3D-protocol for leaching behavior of glass elements.

Results

■ Coating homogeneity

To simulate typical performance for parenteral packaging, baked-on-silicone coated containers were stressed via a typical terminal sterilization method by applying saturated water vapor at 121 °C for 30 min. Even though the coating has a quite homogeneous visual appearance (fig. 1, fig. 1a), top) the interaction with water vapor in the autoclave results in a visible dissolution of the silicone film accompanied with free silicone droplets. Such a phenomenon represents an inherent risk for contamination of the packaged drug product.

The optical reflectometry measures pointed out the lateral dissolution of the baked-on silicone coating more precisely. The original silicone layer with a total thickness of around 230 nm in the mid-body area and the homogeneous thickness distribution along the circumference (fig 1a), bottom) is heavily distorted after the terminal sterilization procedure (fig 1b), bottom). A part of the layer is dissolved and an island-like structure remains on the inner glass surface. The color change in the diagram indicates a thickness reduction from 230 nm down to an inhomogeneous silicone coverage (10–80 nm). Even if the mechanical functionality e.g. gliding properties in the case of syringes or cartridges is only marginally hampered, a hermetic coverage to avoid chemical interactions with glass elements is destroyed and the silicone residues are dissolved in the drug product.

In opposite to the described behavior for siliconized surfaces, PICVD coated containers are far more resistant to terminal sterilization processing. Starting with the characterization of the coated inner vial surface as produced via optical reflectometry, its homogeneity becomes visible (fig. 2, left). The layer thickness in the mid-body area is 127 nm and tend to be thinner in the flange area to values around 60 nm.

To stress the coating, the container was filled with purified water, autoclaved at 121 °C for 60 min and then stored for four months at room temperature. Even so the testing conditions are far harsher in comparison to the siliconized container

Table 1

Results of hydrolytic surface resistance test according European Pharmacopeia 3.2.1.

Status	Condition of Container	Mean value for oxides, expressed as sodium oxide* Na_2O [µg/ml]	Percentage of Pharm. Eur. limit
uncoated	reference container as produced	1.27 ± 0.08	64 %
uncoated	reference container washed and dried	1.19 ± 0.08	60 %
coated	baked-on siliconized container	1.09 ± 0.08	55 %
coated	SiO_2-coated container	0.006 ± 0.006	0.3 %

* according Pharm. Eur. (9.6) chapter 3.2.1 by flame atom adsorption spectroscopy (FAAS); limit value for this container type (2R vial): 2.00 µg/ml; number of samples per test: 20 containers.

Table 2

E&L concentrations of the dissolved "main glass elements" extracted from 10R container (as defined in the manufacturers specification data sheet).

Element	Unit	Method	Uncoated Reference container: SCHOTT TopLine FIOLAX®	SiO_2-coated container: SCHOTT Type I plus®	Measurement uncertainty
Si	µg/ml	ICP-OES	2.0	0.17	15 % if appl.
B	µg/ml	ICP-MS	0.27	< 0.005	n. a.
Al	µg/ml	ICP-MS	0.29	0.033	20 % if appl.
Na	µg/ml	ICP-MS	0.74	0.005	15 % if appl.
Ca	µg/ml	ICP-MS	0.055	< 0.005	30 % if appl.

the inner surface of the SiO_2-layer remained unchanged. The layer is completely homogeneous down to microscopic scale (fig. 2, right).

Leaching behavior/hydrolytic resistance performance

To stress the performance of primary packaging containers to the most important topic, storing drug products with minimal influence of the chosen container, siliconized and PICVD coated containers in comparison to an uncoated reference were analyzed according to the given test procedures for surface hydrolytic resistivity (USP, Pharm. Eur., ISO 4802).

For this purpose, containers were tested with different conditions to work out the influence of the different process steps respective the final container property. To be compliant to the regulatory demands, the limit value of 2.00 µg/ml Na_2O should not be exceeded. This goal is reached for any of the tested samples. However, especially for sensitive drug products the ion release out of the container inner surface is of main interest when it comes to shelf life definition for the drug product. Here the just produced bulk container meets those requirements (64 % of allowed limit) for reference reasons (table 1). The results further confirm the industry wide known fact that the pharmaceutical washing process is able to slightly reduce the amount of released ions (in the frame of the measurement uncertainty), which is often misleadingly attributed to an ion barrier property of the silicone layer. The siliconized container also underwent this process step followed by spray coating and a baked-on process step. The performance increase from 60 % to 55 % of the given limit is also within the measurement uncertainty and more or less insignificant. However, a real performance step can be seen for the inorganic SiO_2-coated container. Here the ion release is practically blocked completely. This also gives first evidence of the significant diffusion barrier of such kind of coating.

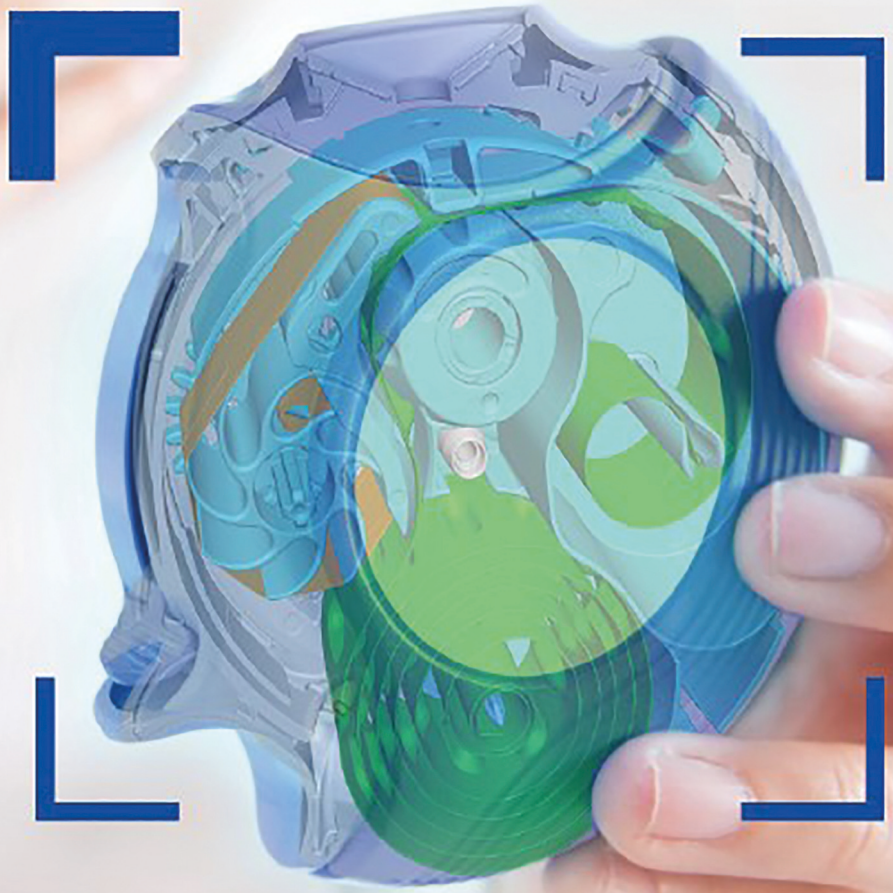
To expand the diffusion barrier function property, a leaching test according ICH/Q3D was performed focusing on the main glass elements. This test was also performed using containers filled with purified water and autoclaved according to the procedure described in the <USP> 660. The eluate was analyzed by means of ICP (table 2).

By comparing the results given for uncoated and SiO_2 coated containers, it is obvious that the coating must be hermetic and prevent leaching of glass elements in a high manner. Only Si as the main element of the coating has a relevant amount of leaching but also here it is more

Pharm. Ind. 82, Nr. 9, 1192–1198 (2020)

Characterize the microstructure of your PCI formation

ZEISS Microscopes for pharma research



ZEISS

www.zeiss.com/life-sciences

Seeing beyond

than a factor of ten lower as for the uncoated glass.

Conclusion

The most important property for a parenteral packaging glass container is the grade of chemical inertness: for the whole period of the predicted shelf life of a specific drug product the interaction/solution of container-components into the pharma product shall be minimized respectively completely avoided. This behavior was investigated for uncoated glass containers as well as for those with baked-on silicone coating or an inorganic SiO_2-coating on the inner container surface to prevent direct interaction with the filled drug product. Due to the nature of the coating application, a big difference in uniformity and homogeneity between spray coated and gas phase coated thin films becomes visible. Even baked-on silicone layers increase other container properties e.g. wetting behavior or mechanical gliding, the functionality for diffusion barrier purposes and prevention of chemical interaction with glass elements cannot be achieved. In opposite, the inorganic SiO_2-coating performs with hermetic surface protection with consequently extreme low dissolution of glass elements over the shelf life of the drug product. This addresses especially the stability of pH of the wet solution due to the avoidance of leaching out ions into the solution.

This behavior is consistent with the paper of A. Chillon et al., who have already reported that siliconized syringes (sprayed-on) and non-siliconized (bulk) syringes will leach comparable amounts of sodium. They performed the test for hydrolytic resistance according EP 3.2.1 and finally concluded, that sprayed-on silicone does not act as a protective layer neither minimizing leachables nor reducing the risk for glass delamination [17].

Acknowledgement

We would like to thank Dr. Andreas Wagner and Dr. Eveline Rudigier-Voigt from SCHOTT AG for valuable support.

REFERENCES

[1] Rothhaar U, Klause M, B. Hladik. Comparative Delamination Study to Demonstrate the Impact of Container Quality and Nature of Buffer System. PDA J Pharm Sci Technol. 2016;70(6):560–567.
[2] Rupertus V, Hladik B, Rothhaar U, Scheumann V. A Quick Test to Monitor the Delamination Propensity of Glass Containers. PDA J Pharm Sci Technol. 2014;68(4);373–380.
[3] Hladik B, Buscke F, Frost R. Comparative Leachable Study of Glass Vials to Demonstrate the Impact of Low Fill Volume. PDA J Pharm Sci Technol. 2019;73(4):345–355.
[4] Frost R, Moseler D, Lange U, et al. Glass processing device and floor-standing machine for producing glass containers. Patent EP 2818454 A1; US 9,796,615 B2.
[5] Bach D, Krause D, editors. Thin Films on Glass. Berlin/Heidelberg/New York: Springer-Verlag; 2003.
[6] Walther M, Rupertus V, Seemann C, et al. Pharmaceutical vials with extremely high chemical inertness. PDA J Pharm Sci Technol. 2002;56(3):124–129.
[7] Funke S, Matilainen J, Nalenz H, et al. Optimization of the bake-on siliconization of cartridges. Part II: Investigations into burn-in time and temperature. Eur. J. Pharm. Biopharm. 2016 Aug;105:209–22.
[8] Mundry T, Schurreit T, Surmann P. Surface Characterization of Polydimethylsiloxane Treated Pharmaceutical Glass Containers by X-ray-excited Photo- And Auger Electron Spectroscopy. Fresenius J. Anal. Chem. 2000;368(8):820–831.
[9] Mundry T, Schurreit T, Surmann P. The fate of silicone oil during heat-curing glass siliconization- changes in molecular parameters analyzed by size exclusion and high temperature gas chromatography. PDA J Pharm Sci Technol. 2000;54(5):383–397.
[10] Jones LS, Kaufmann A, Middaugh CR. Silicone oil induced aggregation of proteins. J. Pharm. Sci. 2005;94(4)918–927.
[11] Krayukhina E, Tsumoto K, Uchiyama S, Fukui K. Effects of Syringe Material and Silicone Pil Lubrication on the Stability of Pharmaceutical Proteins. J. Pharm. Sci. 2015;104(2):527–535.
[12] Majumdar S, Ford BM, Mar KD, et al. Evaluation of the Effect of Syringe Surfaces on Protein Formulations. J. Pharm. Sci. 2011;100(7):2 563–2 573.
[13] Shi GH, Gopalrathnam G, Shinkle SL et al. Impact of Drug Formulation Variables on Silicone Oil Structure and Functionality of Prefilled Syringe System. PDA J Pharm Sci Technol. 2018;72(1):50–61.
[14] Thirumangalathu R, Krishnan S, Speed Ricci et al. Silicone Oil- and Agitation-Induced Aggregation of a Monoclonal Antibody in Aqueous Solution. J. Pharm. Sci. 2009;98(9):3 167–81.
[15] Bai S, Landsman P, Spencer A, et al. Evaluation of Incremental Siliconization Levels on Soluble Aggregates, Submicron and Subvisible Particles in a Prefilled Syringe Product. J. Pharm. Sci. 2016;105(1):50–63.
[16] Boltres B. When Glass meets Pharma, Aulendorf: Editio Cantor Verlag; 2015.
[17] Chillon A, Zuccato D. Introducing the Alba® Primary Packaging Platform. Part 2: Inorganic Extractables Evaluation. PDA J Pharm Sci Technol. 2019;73 (3):235–246.

Correspondence:
Diana Löber
SCHOTT Pharmaceutical Systems
Hattenbergstraße 10
55122 Mainz (Germany)
e-mail: Diana.Loeber@schott.com

Chefredaktion: Claudius Arndt. Sekretariat: Valentina Krinizki. Verlag: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, Baendelstockweg 20, 88326 Aulendorf (Germany). Tel.: +49 (0) 75 25 94 00, Fax: +49 (0) 75 25 94 01 80. E-Mail: redaktion@ecv.de. www.ecv.de. Herstellung: rdz GmbH / Holzmann Druck GmbH & Co. KG.