ARTICLE

Syringe Siliconization

Trends, methods, analysis procedures

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Originally published by ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH as: Petersen, C. Containers Made of Cyclic Olefins as a New Option for the Primary Packaging of Parenterals. Pharm. Ind. 2012;74(1):156-162.

Introduction

Primary packaging for injectables almost exclusively comprises a glass container (cartridge, syringe, vial) and an elastomer closure. Ampoules are an exception.

Elastomers are by nature slightly sticky, so all elastomer closures (plunger stoppers for syringes and cartridges, serum or lyophilization stoppers) are siliconized. Siliconization prevents the rubber closures from sticking together and simplifies processing of the articles on the filling lines. For example, it minimizes mechanical forces when the stoppers are inserted. Siliconization is therefore essential to process capability.

Although syringes and cartridges are always siliconized, this applies to a lesser extent to vials and ampoules. On the container the siliconization provides a barrier coating between the glass and drug formulation. It also prevents the adsorption of formulation components on the glass surface. The hydrophobic deactivation of the surface also improves the containers' drainability. In prefillable syringes and cartridges, siliconization also performs another function. It lubricates the syringe barrel or cartridge body enabling the plunger to glide through it. Siliconization of the plunger stopper alone would not provide adequate lubrication.

Silicone oils are ideal as lubricants because they are largely inert, hydrophobic and viscoelastic. Chemical and physical requirements for lubricants are set out in the relevant monographs of the American (United States Pharmacopoeia, USP) and European (Pharmacopoeia Europaea, Ph. Eur.) pharmacopoeias [1, 2]. Section 3.1.8 of Ph. Eur. also defines a kinematic viscosity of between 1,000 and 30,000 mm2/s for silicone oils used as lubricants [3]. By contrast, the monograph for polydimethylsiloxane (PDMS) in the USP [2] permits the use of silicone oils with a viscosity of 20 to 30,000 centistokes.

However, increasingly stringent quality requirements and new bioengineered drugs are now taking siliconization technology to its limits. Nonhomogenous siliconization which can occur when simple coating techniques are used on longer syringe barrels can, in some cases, lead to mechanical problems. These include the incomplete drainage of the syringe in an auto-injector or high gliding forces. Silicone oil droplets are always observed in filled syringes.

The number of silicone oil droplets increases in line with the quantity of silicone oil used. Droplets which are visible to the naked eye could be viewed as a cosmetic defect. At subvisual level, the issue of whether silicone oil particles could induce protein aggregation is currently under discussion [4].

In light of this development, there is an obvious trend towards optimized or alternative coating techniques. Attempts are being made to achieve the most uniform possible coating with a reduced quantity of silicone oil and to minimize the amount of free silicone oil by way of baked-on siliconization. In this context, reliable analysis technologies that can be used to make qualitative and quantitative checks on the coating are absolutely essential.

Alternative coating techniques are also being developed.

Silicone oils and their properties

Silicone oils have been used for half a century in numerous pharmaceutical applications. For example, they are used as lubricants in pharmaceutics production and as inert pharmaceutical base materials (e.g. soft capsule walls) [5]. Trimethylsiloxy endblocked polydimethylsiloxane (PDMS, dimethicone) in various viscosities is generally used for siliconization (Fig. 1).

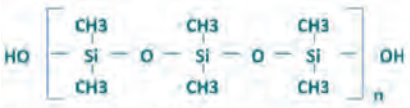

Fig. 1: Polydimethylsiloxane.

The most frequently used silicone oil for the siliconization of primary packaging components is DOW CORNING® 360 Medical Fluid, which has a viscosity of 1,000 cSt. PDMS is produced by reducing quartz sand to silicone metal. In the next step, the silicone reacts directly with methyl chloride in a process called MüllerRochow synthesis to create methyl chlorosilanes. In this process, a mixture of different silanes is produced, the majority of which (75%–90%) are dimethyldichlorosilane (CH3)2 SiCl2.

After distillative separation, the dimethyldichlorosilane is converted by hydrolysis or methanolysis into silanols which condense into lowmolecular-weight chains and cycles.

In an acidic (cationic) or alkaline (anionic) catalyzed polymerization, polydimethylsiloxanes with hydroxy functions are generated. After the addition of trimethylchlorosilane they are furnished with trimethylsiloxy end groups. The short chain molecules are removed from the resulting polydisperse polymers by way of vaporization, leaving deployable PDMS.

The characteristic aspect of the PDMS molecule is the Si-O bond.

With a bond energy of108 kcal/mol, it is considerably more stable than the C-O bond (83 kcal/mol) or the C-C bond (85 kcal/mol). PDMS is accordingly less sensitive to thermal loads, UV radiation or oxidation agents. Reactions such as oxidation, polymerization or depolymerization do not occur until temperatures exceeding 130 °C. The molecule also typically has a flat bond angle (Si-OSi 130 °C) which has low rotation energy and is especially flexible (Fig. 2). A high bond length(1.63Å Si-O as compared to 1.43Å for C-O) makes the molecule comparatively gas-permeable [6].

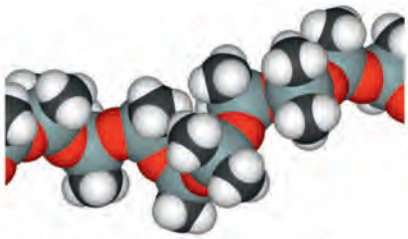

Fig. 2: 3D-structure of polydimethylsiloxane.

The spiral shaped (and therefore easily compressible) molecule is surrounded by CH3 groups which are responsible for the chemical and mechanical properties of PDMS. The molecule's methyl groups only interact to a very limited extent. This ensures low viscosity, even with high molecular weights, which simplifies the distribution of PDMS on surfaces and makes it a very effective lubricant. PDMS is also largely inert and reactions with glass, metals, plastics or human tissues are minimal. The CH3 groups make PDMS extremely hydrophobic. It is insoluble in water, but soluble in non-polar solvents [6].

Siliconized syringes

As already explained the syringe system only works if the glass barrel and plunger stopper siliconization are homogenous and optimally harmonized. For needle syringes, siliconization of the needle is also essential to prevent it sticking to the skin, thereby minimizing injection pain.

For the so-called oily siliconization of the syringe glass barrel DOW CORNING® 360 with a viscosity of 1,000 cSt is used. The DOW CORNING® 365 siliconization emulsion is often used in the baked-on siliconization process. The needle is siliconized using a wipe technique during ready-to-fill processing. DOW CORNING® 360 with a viscosity of 12,500 cSt is used. Another option is the thermal fixation of silicon oil on the needle during the needle mounting process.

The goal of syringe barrel siliconization is to obtain the most even anti-friction coating possible along the entire length of the syringe in order to minimize break loose and gliding forces when the plunger stopper is deployed (Fig. 3).

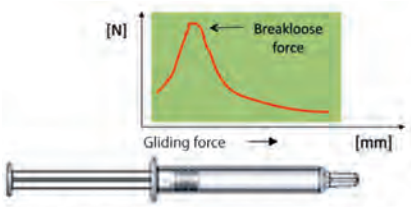

Fig. 3: Extrusion force profile of a prefillable syringe.

Inadequate siliconization of the syringe barrel, particularly the existence of unsiliconized areas, can cause slip-stick effects that impair the syringe's function. The forces in the injection process can then be too high or the entire system can fail.

Since inadequate siliconization and gaps in the coating are often found on the lower end of the syringe (luer tip/needle end), it is possible that the syringe will not be completely emptied. Such defects can remain undiscovered, particularly in auto-injectors since these are closed systems.

The result could be that an inadequate dosage of the medication is administered.

The obvious solution is to increase the amount of silicone oil used to achieve a homogenous coating. However, as already mentioned, increasing the amount of silicone oil used is also associated with higher quantities of silicone particles in the solution. With protein-based drugs, in particular, undesirable interactions with silicone oil particles cannot be ruled out. Sub-visual silicone oil particles are thought to promote protein aggregation which can increase the severity of immune responses and reduce the drug's tolerability. However, the underlying mechanism is not yet fully understood. There is a discussion as to whether protein aggregation is influenced by additional motion, e.g. shaking the syringe [7].

Experiments have also shown that when silicone oil in excess of 1 mg/ syringe is used the additional silicone oil does not further reduce gliding forces.

The interior siliconization of glass syringe barrels has another advantage. It prevents the drug solution from interacting with the glass surface and rules out related problems such as the loss of active ingredients through adsorption or pH value changes due to alkali leaching. Prefillable glass syringes are only manufactured from high quality type 1 borosilicate glass. However, sodium ions can still leach out of the glass surface if the syringe contains an aqueous solution and is stored for a long period of time. This leads to higher pH values which could be problematic in unbuffered systems.

Acidic environments foster this process.

$$Si\text{-}O\text{-}Na + H_2O \longleftrightarrow SiOH + NaOH$$

In alkaline environments, on the other hand, an etching process is observed.

$$2NaOH + (SiO_2)X \longrightarrow Na_2SiO_3 + H_2O$$

Aqueous solutions with a high pH value cannot therefore be stored for long periods of time in borosilicate glass containers. They have to be lyophilized and reconstituted before use. In extreme cases, the etching of the glass surface can cause delamination. Hydrophobic

deactivation of the container by siliconization effectively protects the glass surface.

Optimized siliconization

For the above-mentioned reasons, the main objective in siliconization is to achieve the most homogenous possible coating with the minimum possible quantity of silicone oil. Initially it is necessary to establish the minimum quantity of silicone oil which will reliably satisfy the quality requirements of the application. In the production of ready-to-fill syringes, siliconization generally takes place after washing and drying. Fixed nozzles positioned at finger flange level under the syringe barrel spray the silicone oil onto the inside surface. In long syringes, the silicone oil is sometimes unevenly distributed and the concentration of the silicone oil is lower at one end of the syringe (luer tip/needle end). The use of diving nozzles can considerably improve the evenness of the coating across the entire length of the syringe body. In this process, the nozzles are inserted into the syringe to apply the silicone oil (finely atomized) in motion. The result is practically linear as is shown by the closely bundled gliding forces in the force path diagram (Fig. 4).

Studies on 1 ml long syringes have revealed considerable potential for reducing the amount of silicone oil required. In the experiment, the quantity of silicone oil per syringe could be reduced by 40 % without any impairment of the system's functional properties (Fig. 5). In practice the calculation of the optimum quantity of silicone oil has to take syringe volume, plunger stopper type (coated/ uncoated), plunger stopper placement method (seating tube/ vacuum) and application requirements (injection systems) into account. Plunger stoppers from different suppliers not only differ in terms of the type of rubber used and their design, they are also coated with silicone oils of different viscosities. The siliconization methods also differ considerably. These variables can have a bigger impact on the syringe system's functional properties than the syringe siliconization of different suppliers, as shown by Eu et al. [8].

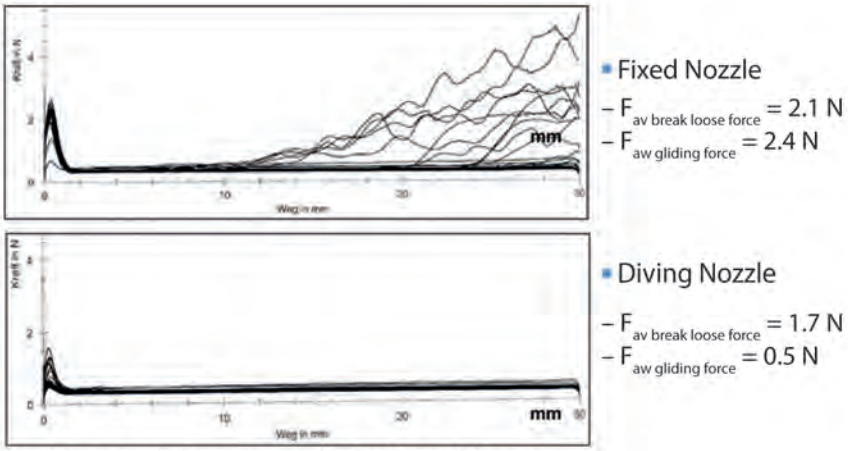

Fig. 4: Comparison of extrusion force profiles diving nozzle vs. fixed nozzle.

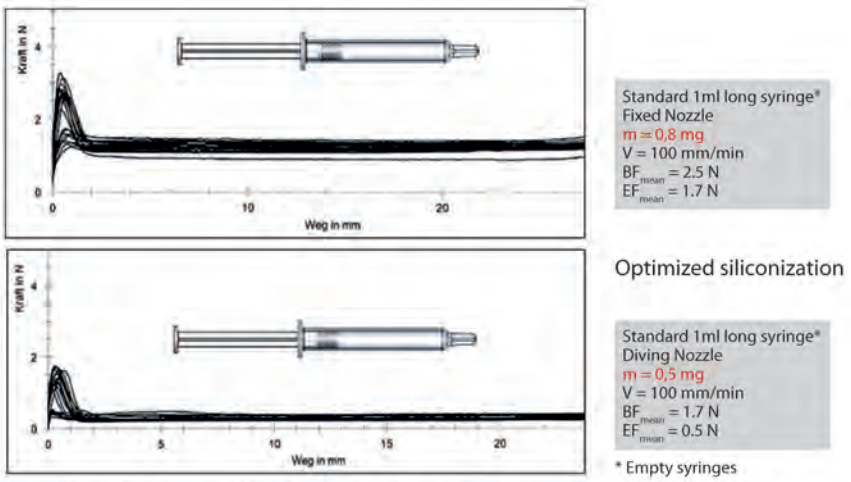

Fig. 5: Extrusion force profile after optimized siliconization.

Baked-on siliconization

Another key advancement in siliconization technology is the baked-on siliconization technology. It involves the application of silicone oil as an emulsion which is then baked on to the glass surface in a special kiln at a specific temperature and for a specific length of time.

In the baked-on process, both hydrogen and covalent bonds form between the glass surface and the polydimethylsiloxane chains. The bonds are so strong that part of the silicone oil cannot be removed with solvent and a permanent hydrophobic layer is created (Fig. 6). In addition the average molecule weight increases as a result of polymerization and the vaporization of short chain polymers. The resulting, extremely thin layer of silicone in conjunction with the low quantity of silicone oil used in the emulsion minimizes free silicone in the syringe and ensures that the required quality of finish is achieved. The layer thickness measures 15–50 nm. By comparison, the average layer thickness with oily siliconization is 500–1,000 nm.

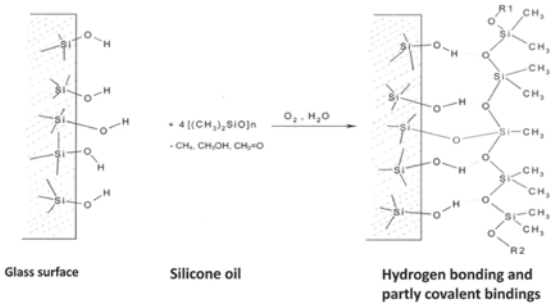

Fig. 6: Baked-on siliconization.

Baked-on siliconization reduces the measurable quantity of free silicone oil to approx. 10 % of the normal value. As a result, there are fewer sub-visual and visual silicone oil particles in the solution. This siliconization process is therefore recommended for use with sensitive protein formulations. It is also advantageous for ophthalmological preparations which are associated with very stringent requirements as regards particle contamination.

Another benefit is the stability of the mechanical properties of the filled syringe throughout its shelf life.

The ribs of a plunger stopper press into the silicone layer when a syringe with oily siliconization is stored for long periods of time and the glass comes into direct contact with the rubber. Since elastomers are always slightly sticky, the break loose forces increase over the storage period.

With baked-on siliconization, however, this phenomenon is not observed to the same extent (Fig. 7). The break loose force remains practically constant over the entire storage period.

Analysis methods

The optimization of the siliconization process necessitates reliable qualitative and quantitative analysis methods. Online methods for the one-hundred percent control of siliconization during production are not currently available. In process control, random samples are taken and several destructive and non-destructive methods are used.

In the glass dust test, the siliconization is made visible by dusting it with finest glass particles (Fig. 8).

Fig. 8: Glass dust test: left – syringe siliconized with an diving nozzle, right – syringe siliconized with a fixed nozzle.

This destructive method is simple but time-consuming. It is also associated with the problems that the quality of the siliconization is subjectively evaluated and the results are affected by temperature and air humidity.

Measuring the gliding force is an indirect method of determining the evenness of the siliconization (Fig. 9). This process is also destructive and associated with problems.

For example, the results are influenced by the positioning of the plunger stopper and there is no standard for extrusion speed. A value of 100 mm/min is often taken for empty syringe systems; and up to 380 mm/min. for filled systems.

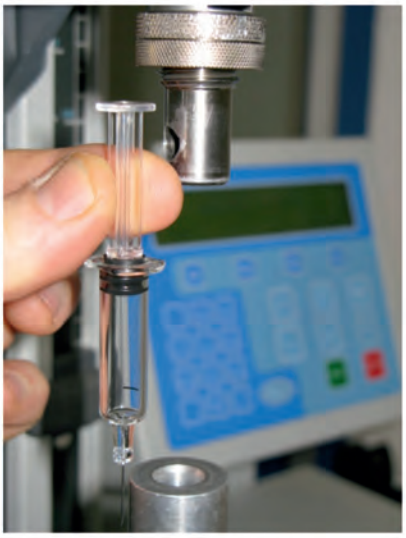

Fig. 9: Gliding force measurement.

Relatively fast quantitative and non-destructive results can be obtained with reflexometry. For example, the Layer Explorer UT (Fig. 10) which is manufactured by rapID scans the syringe body line-by-line. It can measure layer thicknesses of 15 nm to several thousand nm with a precision of 5 nm (Fig. 10.1). Scanning a 40 mm syringe with the Layer Explorer takes approximately 1 minute.

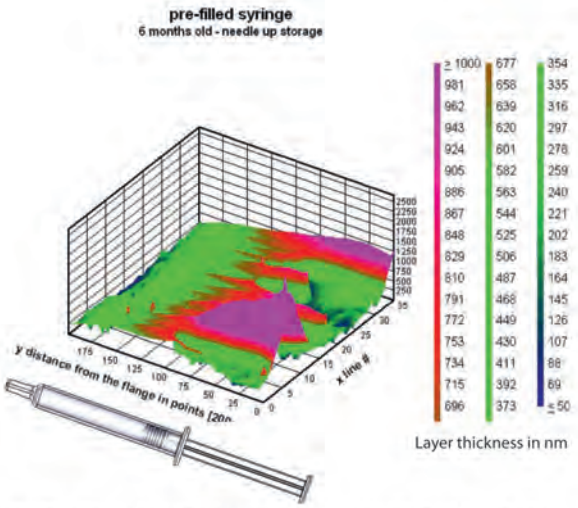

Fig. 10: Silicone layer thickness measurement with the Layer Explorer RapID (own data).

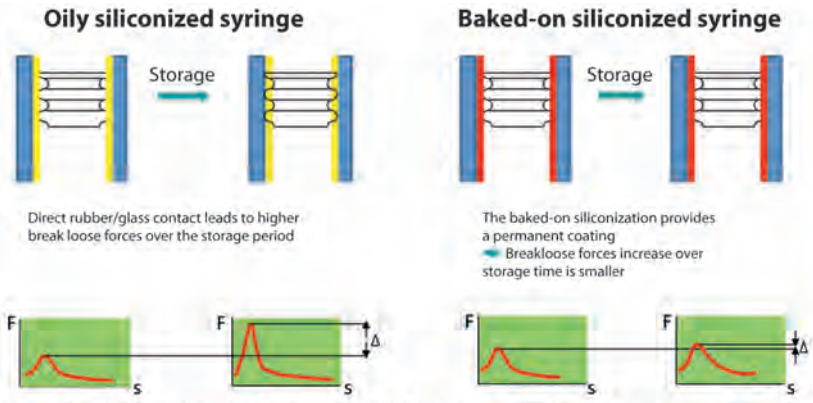

Fig. 7: Comparison of syringes with oily and baked-on siliconization.

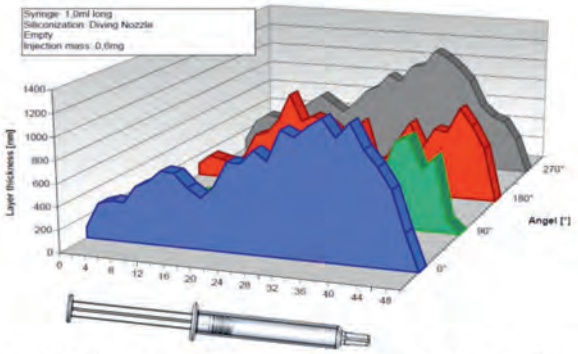

Fig. 10.1: Silicone layer thickness measurement with the Layer Explorer (own data).

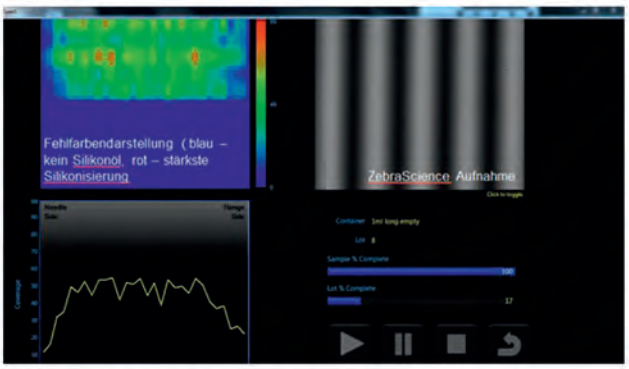

Fig. 11: ZebraScience visualization of siliconization.

Fig. 11.1: Visualization of syringe barrel siliconization (Source: Zebra Science).

Another non-destructive technique such as the one developed by Zebra Science (Fig. 11) is based on digital image processing. The entire inside surface of the syringe barrel is imaged to visualize typical siliconization surface structures. The technology captures these visual cues as a direct indication of silicone oil presence and poorly siliconized areas (Fig. 11.1). It delivers fast qualitative results and is suitable for empty and filled syringes. However, empty syringes should be measured immediately after siliconization because even just half an hour after siliconization the distribution of the silicone provides a completely different picture and it takes a very experienced person to interpret the results properly.

Unfortunately, this method is also not fast enough to facilitate 100 % online control during the washing and siliconization process.

Outlook

There is a trend towards reduced-silicone systems or baked-on siliconization in glass syringe finishing. Improved analysis techniques and a better understanding of the phenomena involved support optimized use of silicone oil.

New issues are arising as a result of the use of innovative materials or coatings. In light of the increasing complexity of devices and the more widespread incidence of biopharmaceuticals with specific requirements, new alternative materials for primary packaging products are becoming increasingly interesting. For example, the inside surfaces of vials and syringes can be coated with pure SiO2 in a plasma process to minimize their interaction with drugs. Plastic systems based on cyclic olefins (COP/COC) are also gaining in significance for prefilled syringes and vials. COP syringes such as the ClearJect TasPack by Taisei Kako Co. Ltd have glass-like transparency. Additionally, they have a higher break resistance, their pH stability range is larger and there is no metal ion leaching. Excellent dosage precision is also very important in packaging for bio-pharmaceuticals.

In most cases siliconization is also essential in COP syringes. Silicone oil-free systems are a brand new approach. The gliding properties of the fluoropolymer coating on specially developed plunger stoppers eliminate the need to siliconize plastic syringes. There are as many innovative ideas for the development of primary packaging products as there are innovative drugs and syringe systems. ■

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