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I, Angela Hirons-Goulbourn, hereby certify that the following proofreading is, to the best of my knowledge and belief, a true and accurate translation from German to English of the file "Exhibit 1064, Bruno Reuter and Claudia Petersen. "Die Silikonisierung von Spritzen: Trends, Methoden, Analyseverfahren," TechnoPharm 2, Nr. 4 (2012): 238-244". I declare that I am fluent in German, and further declare that all statements herein of my own knowledge are true, and all statements made on information and belief are believed to be true, and these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both under Section 1001 of Title 18 of the United States Code. I declare under penalty of perjury that the foregoing is true and correct.

A. Hirons. Goulbourn.

Angela Hirons-Goulbourn
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Techno Pharm

Focus Packaging

Syringe Siliconization

Trends, methods, analysis procedures

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Summary

Ready-to-fill, i.e. sterile, prefillable glass syringes, are washed, siliconized, sterilized and packaged by the primary packaging manufacturer. They can then be filled by the pharmaceutical companies without any further processing. These days the majority of prefillable syringes are made of glass and the trend looks set to continue. The siliconization of the syringe barrel is an extremely important aspect of the production of sterile, prefillable glass syringes because the functional interaction of the glass barrel siliconization and the plunger stopper siliconization is crucial to the efficiency of the entire system. Both inadequate and excessive siliconization can cause problems in this regard. The use of modern technology can achieve an extremely uniform distribution of silicone oil in glass syringes with reduced quantities of silicone oil. Another option for minimizing the amount of free silicone oil in a syringe is the thermal fixation of the silicone oil on the glass surface in a process called baked-on siliconization.
Plastic-based silicone oil-free or low-silicone oil prefillable syringe systems are a relatively new development. Silicone oil-free lubricant coatings for syringes are also currently in the development phase.

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 mm^2/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

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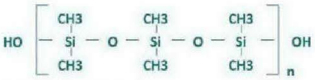


$HO-[Si(CH_3)_2-O-Si(CH_3)_2-O-Si(CH_3)_2]_n-OH$

Fig. 1: Polydimethylsiloxane.

drugs are now taking siliconization technology to its limits. Non-homogenous 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 sub-visual 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 end-blocked polydimethylsiloxane (PDMS, dimethicone) in various viscosities is generally used for siliconization (Fig. 1).

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 Müller-Rochow synthesis to create methyl chlorosilanes. In this process, a mix ture of different silanes is produced, the majority of which (75%–90%) are dimethyldichlorosilane $(CH_3)_2SiCl_2$. After distillative separation, the di-methyldichlorosilane is converted by hydrolysis or methanolysis into silanols which condense into low- molecular-weight chains and cycles. In an acidic (cationic) or alkaline (an- ionic) 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 of 108 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-O- Si 130 °C) which has low rotation energy and is especially flexible (Fig. 2). A high bond length (1.63 Å Si-O as compared to 1.43 Å for C-O) makes the molecule comparatively gas-permeable [6].

The spiral shaped (and therefore easily compressible) molecule is surrounded by CH_3 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 CH_3 groups make PDMS extremely hydrophobic. It is insoluble in water, but soluble in non-polar solvents [6].

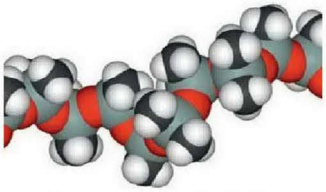


Fig. 2: 3D-structure of polydimethylsiloxane.

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 COR- NING® 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 silicone 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 breakloose and gliding forces when the plunger stopper is deployed (Fig. 3).

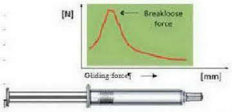


Fig. 3: Extrusion force profile of a prefillable syringe.

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. How- ever, 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 tage. It prevents the drug solution from interacting with the glass sur- face 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.

$$Si\text{-}O\text{-}Na + H20 \leftrightarrow SiOH + NaOH$$

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

$$2NaOH + (SiO2)X \rightarrow Na2SiO3 + H2O$$

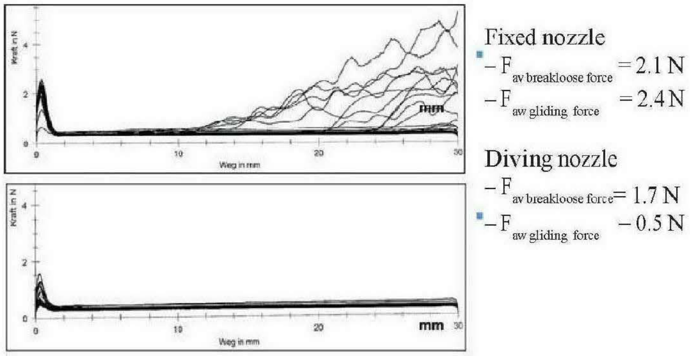
Aqueous solutions with a high pH value cannot therefore be stored for long periods of time in borosilicate glass containers. They have to be lyophilized and reconstituted before use. In extreme cases, the etching of the glass surface can cause delamination. Hydrophobic deactivation of the container by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



m = 0.8 mg, v = 300 mm/min, empty 1 ml long LC syringes

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

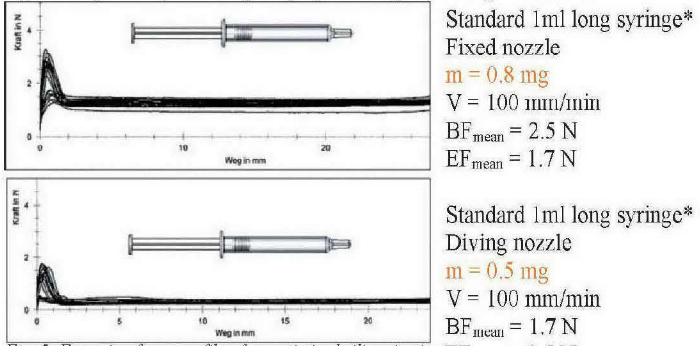


Fig. 5: Extrusion force profile after optimized siliconization.

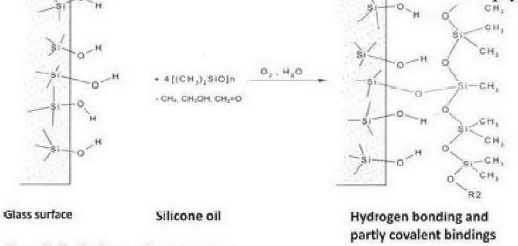


Fig. 6: Baked-on siliconization.

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 be- tween 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.

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, how- ever, this phenomenon is not observed to the same extent (Fig. 7). The breakloose force remains practically constant over the entire storage period.

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