In this paper, Bruno Reuter, Director of Product Development, and Claudia Petersen, Director, Business Development, both of Gerresheimer Bünde, provide a detailed description of silicone oil and its applications in syringe siliconisation, highlighting the advantages and challenges siliconisation brings to the drug formulation and recent developments in the field.

Ready-to-fill, i.e. sterile, prefilled glass syringes, are washed, siliconised, sterilised and packaged by the primary packaging manufacturer. They can then be filled by pharmaceutical companies without any further processing. These days the majority of prefilled syringes are made of glass and the trend looks set to continue. The siliconisation of the syringe barrel is an extremely important aspect of the production of sterile, prefilled glass syringes because the functional interaction of the glass barrel siliconisation and the plunger stopper siliconisation is crucial to the efficiency of the entire system. Both inadequate and excessive siliconisation can cause problems in this connection. 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 minimising 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 siliconisation. Plastic-based silicone oil-free, and low-silicone oil, prefilled syringe systems are relatively new developments. 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 lyophilisation stoppers) are siliconised.

Siliconisation prevents the rubber closures from sticking together and simplifies processing of the articles on the filling lines. For example, it minimises mechanical forces when the stoppers are inserted. Siliconisation is therefore essential to process capability.

Although syringes and cartridges are always siliconised, this applies to a lesser extent to vials and ampoules. On the container the siliconisation 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 prefilled syringes and cartridges, siliconisation also performs another function. It lubricates the syringe barrel or cartridge body enabling the plunger to glide through it. Siliconisation 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 US Pharmacopeia (USP) and the European Pharmacopoeia (Ph Eur). Section 3.1.8 of the Ph Eur also defines a kinematic viscosity of 1,000-30,000 mm²/s for silicone oils used as lubricants. In contrast, the monograph for polydimethylsiloxane (PDMS) in the USP 2 permits the use of silicone oils with a viscosity of 20-30,000 centistokes (cSt).

However, increasingly stringent quality requirements and new bioengineered drugs are now taking siliconisation technology to its limits. Non-homogenous siliconisation, 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 optimised or alternative coating techniques. Attempts are being made to achieve the most uniform possible coating with a reduced quantity of silicone oil and to minimise the amount of free silicone oil by way of baked-on siliconisation. 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 & 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).3 Trimethylsiloxy end-blocked polydimethylsiloxane (PDMS, dimethicone) in various viscosities is generally used for siliconisation (see Figure 1).

The most frequently used silicone oil for the siliconisation of primary packaging components is DOW CORNING® 360 Medical Fluid. PDMS is produced by reducing quartz sand to elemental silicon. In the next step, the silicon reacts directly with methyl chloride in a process called Müller-Rochow synthesis to create methyl chlorosilanes. In this process, a mixture of different silanes is produced, the majority of which (75%–90%) are dimethyldichlorosilane (CH₃SiCl₂). After distillative separation, the di- or methyldichlorosilane is converted by hydrolysis or methanolysis into silanols which condense into low-molecular-weight chains and cycles.

In an acidic (cations) or alkaline (anions) catalysed polymerisation, polydimethylsiloxanes with hydroxyl functions are generated. After the addition of trimethylchlorosilane they are furnished with trimethylsiloxyl end groups. The short-chain molecules are removed from the resulting polydisperse polymers by way of vapourisation, 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, polymerisation or depolymerisation do not occur until temperatures exceeding 130°C. The molecule also typically has a flat bond angle (θSi-O-Si = 151° ±12°) which has low rotation energy and is especially flexible (Figure 2). A high bond length (1.63 Å Si−O as compared with 1.43 Å for C−O) makes the molecule comparatively gas-permeable.

The spiral shaped (and therefore easily compressible) molecule is surrounded by CH₂ 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 CH₂ groups make PDMS extremely hydrophobic. It is insoluble in water, but soluble in non-polar solvents.

SILICONISED SYRINGES

As already explained the syringe system only works if the glass barrel and plunger stopper siliconisation are homogenous and optically harmonised. For needle syringes, siliconisation of the needle is also essential to prevent it sticking to the skin, thereby minimising injection pain. For the so-called oily siliconisation of the syringe glass barrel DOW CORNING® 360 with a viscosity of 1,000 cSt is used. The DOW CORNING® 365 siliconisation emulsion is often used in the baked-on siliconisation process (describe later). The needle is siliconised 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 siliconisation is to obtain the most even anti-friction coating possible along the entire length of the syringe in order to minimise break loose and gliding forces when the plunger stopper is deployed (Figure 3).

Inadequate siliconisation of the syringe barrel, particularly the existence of unsiliconised 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 siliconisation 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.

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 siliconisation of glass syringe barrels has another advantage. It prevents the drug solution from interacting with the glass surface and minimises 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-O-Na + H₂O ⇌ SiOH + NaOH

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

2NaOH + (SiO₂)₄ → Na₂SiO₃ + H₂O

Aqueous solutions with a high pH value cannot therefore be stored for long periods in unsiliconised borosilicate glass containers. They have to be lyophilised and reconstituted before use. In extreme cases, the etching of the glass surface can cause delamination. Hydrophobic deactivation of the container by siliconisation effectively protects the glass surface.

OPTIMISED SILICONISATION

For the abovementioned reasons, the main objective in siliconisation is to achieve the most homogeneous 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, siliconisation 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 atomised) in motion. The result is practically linear as is shown by the closely bundled gliding forces in the force path diagram (Figure 4).

Studies on 1 ml long syringes have revealed considerable potential for reducing the amount of silicone oil required. In one experiment, the quantity of silicone oil per syringe could be reduced by 40% without any impairment of the system’s functional properties (see Figure 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 siliconisation methods also differ considerably. These variables can have a bigger impact on the syringe system’s functional properties than the syringe siliconisation of different suppliers, as shown by Eu et al.²

BAKED-ON SILICONISATION

Another key advancement in siliconisation technology is the baked-on siliconisation 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 (Figure 6).
In addition the average molecule weight increases as a result of polymerisation and the vaporisation of short chain polymers. The resulting extremely thin layer of silicone, in conjunction with the low quantity of silicone oil used in the emulsion, minimises 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 siliconisation is 500-1,000 nm.

Baked-on siliconisation reduces the measurable quantity of free silicone oil to approximately 10 % of the normal value. As a result, there are fewer sub-visible and visual silicone oil particles in the solution. This siliconisation 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 siliconisation 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 siliconisation, however, this phenomenon is not observed to the same extent (Figure 7). The break-loose force remains practically constant over the entire storage period.

OUTLOOK

There is a trend towards reduced-silicone systems or baked-on siliconisation in glass syringe finishing. Improved analysis techniques and a better understanding of the phenomena involved support optimised 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 minimise 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 from Kako Co Ltd (Osaka, Japan) 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 siliconisation 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 silicone plastic syringes. There are as many innovative ideas for the development of primary packaging products as there are innovative drugs and syringe systems.

REFERENCES

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