THE EVOLUTION OF FLUOROPOLYMER **COATINGS** FOR PARENTERAL PACKAGING

Set against a background of changing requirements and expectations of syringe components, with reference to biologic formulations, Susan M. Dounce, PhD, Senior Manager, Business Development & Innovation, Injection Systems, Datwyler Pharma Packaging, describes how plunger coating has become about more than barrier properties and, compared with siliconisation, describes how the established Omniflex fluoropolymer coating provides numerous advantages and benefits across the board in prefilled syringes from commercial, to formulation stability and quality, to the end-user experience.

In the conservative, data-driven industry of parenteral packaging, market trends indicate a growing demand for fluoropolymer coated elastomeric closures, primarily to mitigate risks related to drug stability and compatibility. To meet the evolving needs of the biologics industry, the Omniflex fluoropolymer coating is the first coating simultaneously to provide barrier properties and to eliminate the closure as a source of silicone-oil-based subvisible particles (SbVPs). As a consequence of the coating's chemical composition and method of application, Omniflex Coated Plungers (OmniflexCP®) not only have barrier properties that result in superior chemical compatibility but have the added benefits of a significant reduction in SbVP levels and highly consistent delivery forces. OmniflexCP® continues to find broad applicability to address stability, compatibility, and performance challenges, in and beyond the world of biologics.

> "Reducing rubber leachables, while critical, is no longer the sole driver for coated closure development, and it is no longer enough to meet the needs of biologic drug packaging"

THE EVOLVING NEEDS OF BIOLOGICS PACKAGING

A growing preference for fluoropolymer coated elastomers

As the scrutiny over leachables from primary packaging components continues to escalate, so will the demand for fluoropolymer coated elastomeric closures. Traditionally, the design of film-coated closures has focused only on barrier properties. The sole function of the fluoropolymer film coating is to provide an inert barrier between the rubber and the drug formulation, especially for sensitive biologic drugs. The efficacy of therapeutic proteins can depend sensitively on their exact chemical make-up and three dimensional conformation. Interactions with leachables can lead to chemical and/or conformational changes and degradation and/or aggregation, possibly rendering the protein ineffective or immunogenic. Thus, the majority of biologics manufacturers opt for fluoropolymer coated closures.

The most well-known example highlighting the value of fluoropolymer barrier coatings is that of Eprex® (recombinant human erythropoietin alpha) in prefilled syringes. In 1998, a number of

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Eprex® products were reformulated using polysorbate 80 as a stabiliser instead of human serum albumin. Not long after those changes, the incidence of antibody-mediated pure red cell aplasia increased substantially in chronic kidney disease patients treated with Eprex® subcutaneous injections.[1] The immunogenic reactions were judged to be caused by organic leachables from uncoated rubber syringe plungers whose levels were increased by the reformulation with polysorbate 80. The leachables were believed to be acting as adjuvants which increased the immunogenicity of Eprex®. As a result, currently all Eprex® prefilled syringes use fluoropolymer film-coated plungers, and the industry has a heightened awareness of the potential for leachables to modulate an immune reaction towards biologic drugs.[1]

Beyond rubber leachables: Scrutiny over particulate matter increases

The increased scrutiny over particulate matter in parenteral drugs has been fuelled in recent years by regulatory recalls. Approximately half of the US FDA's 2013 issued recalls of parenterals were due to visible particulate matter, ranging from foreign matter (i.e. glass, or metal) to drug-related particles (i.e. crystallised or aggregated protein).[2]

While larger particulates have long been a concern due to their potential for blood vessel occlusion, SbVPs in therapeutic protein formulations have more recently begun to receive increased regulatory oversight. Although much is still unknown about the link between protein aggregates and immunogenicity, there is nonetheless concern over the possible correlation.[3] New regulations will continue to intensify the scrutiny around particle detection and characterisation, and as an example, in August 2014, the FDA issued a guidance on immunogenicity assessment which states:

"It is critical for manufacturers of therapeutic protein products to minimise protein aggregation to the extent possible. This can be done by [among other things]… choosing a formulation and container closure that minimises aggregation during storage." [4]

Elastomeric closures can contribute to particle levels both directly (from silicone oil and particles from the manufacturing processes / environment) and indirectly (from silicone oil or leachables or other particulates, acting as catalysts or nucleation sites for the formation of drug-related particles). Since leachables can potentially cause protein aggregation,[5] the aforementioned guidance appears to support the use of barrier-coated elastomeric closures. However, the increased scrutiny over SbVPs has implications beyond controlling leachables.

Thus, more SbVPs in a protein formulation means more characterisation and risk assessment activities will be required.

Aside from additional characterisation work, formulation delays can occur if a protein is found to be sensitive to aggregation in the presence of silicone oil. The adsorption / desorption of biologics at aqueous-silicone interfaces can cause non-native structural conformations to arise and protein aggregates to form.[8,9] The nucleation of proteins at silicone particle interfaces is a known degradation pathway for some biologics and can result in diminished drug efficacy.[10] These phenomena are exacerbated at high silicone concentrations, when an additional aggressor like heat or agitation is involved, and as modern formulations approach the drugs' solubility limits.[11,12]

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Barrier properties alone are no longer sufficient to address the needs of biologics packaging

Reducing rubber leachables, while critical, is no longer the sole driver for coated closure development, and it is no longer enough to meet the needs of biologic drug packaging. Particularly, silicone oil, and its direct and indirect contributions to particle levels, has become both a significant nuisance and a legitimate concern.

Traditionally, prefilled syringe plungers are siliconised with a 350-1000 cSt silicone oil for three purposes:

(1) to prevent sticking between plungers during shipping / storage
(2) to enable machinability / placement of the plunger into the syringe
(3) to ensure optimal syringe delivery forces.

Even partially film-coated plungers, must be siliconised for these three reasons.

Although its toxicological profile is generally considered to be safe,[6] silicone oil is a significant contributor to SbVP levels in prefilled syringes.[7] High levels of SbVPs in biologic drugs can mean additional characterisation will be required to identify the nature of the particles. Since protein aggregates can potentially present a danger to the patient and diminished efficacy of the drug, the FDA stresses the need for characterising SbVPs in therapeutic protein formulations:

"Assessment should be made of the range and levels of subvisible particles (2-10 µm) present in therapeutic protein products initially and over the course of the shelf life… Sponsors should conduct a risk assessment of the impact of these particles on the clinical performance of the therapeutic protein product." [4]

Silicone oil can lead to delays in the time-to-market due to the potential for additional characterisation and/or formulation work. Furthermore, the interaction of proteins with silicone oil presents a risk to the safety and efficacy of therapeutic proteins. Therefore, for coated elastomeric closures, barrier properties alone are no longer sufficient to meet the needs of the biologics industry. The closures should also reduce or eliminate the levels of silicone oil which can migrate into the drug formulation.

OMNIFLEXCP®: BARRIER-COATED PLUNGERS

The Omniflex coating technology has withstood the test of time with 20 years of commercial sales and filings with every major global regulatory agency. OmniflexCP®, which was launched in 2009 and is currently used with commercial drugs, was the first coated syringe plunger to not only provide barrier properties but also eliminate the need for plunger siliconisation. Today, OmniflexCP® is the best performing fluoropolymer-coated plunger technology that addresses the compatibility and performance challenges of the biologics industry and beyond.

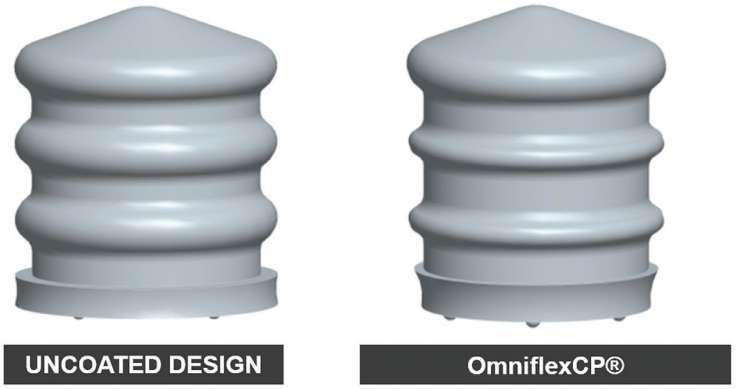

Figure 1: Three dimensional renderings of the 1 mL long uncoated (left) and OmniflexCP® (right) plunger designs.

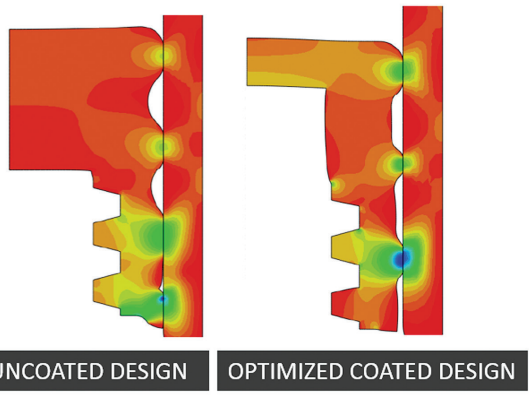

Figure 2: FEA simulations of the compressive stress profiles of the 1-3 mL uncoated (left) and OmniflexCP® (right) plunger designs.

OMNIFLEX COATING TECHNOLOGY

Omniflex (which is a general term to describe several product classes including OmniflexCP® [syringe plungers], OmniflexPlus® and Omniflex3G® [vial stoppers]) is a proprietary, flexible fluoropolymer spray coating that is applied to bromobutyl vial stoppers and syringe plungers and which is designed with two objectives: (1) to be an inert barrier to organic molecules, and metal ions and (2) to impart a low coefficient of friction and thereby eliminate siliconisation.

The OmniflexCP® coating, which is designed to be approximately 20 µm thick, is formed in a two-step process. First, the proprietary fluoropolymer film is applied by a tumble spray coating, and second, a post-treatment process provides sufficient thermal energy to bond the coating covalently to the bromobutyl substrate and to form a smooth, continuous fluoropolymer film. Due to the line-of-sight nature of the spray coating, the entire plunger surface is covered except for the interior of the plunger-rod cavity. The total coverage by the Omniflex coating is in contrast to the partial coverage of most film coatings and has the benefit of providing a complete barrier. The total coverage of the lubricious coating also eliminates the need for siliconisation of the plunger rills. Furthermore, the spray-coating process lends itself to coating custom designs easily for innovative drug delivery devices.

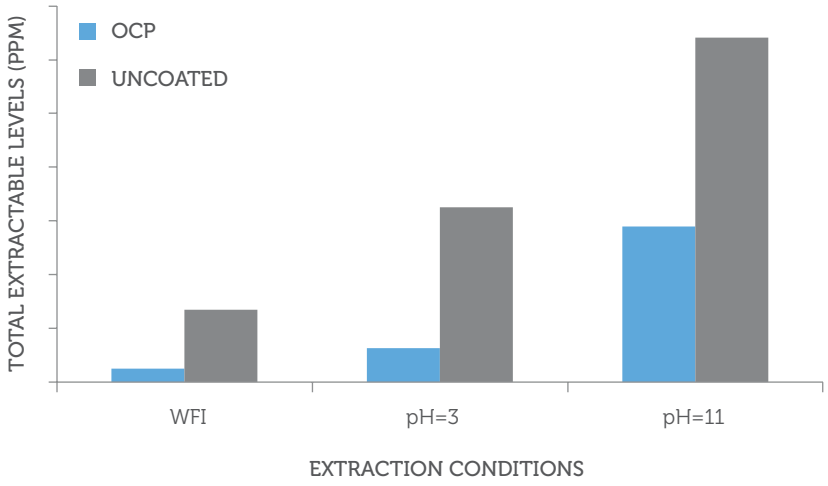

Figure 3: Relative extractable levels from an uncoated bromobutyl (gray bars) compared with OmniflexCP® (blue bars).

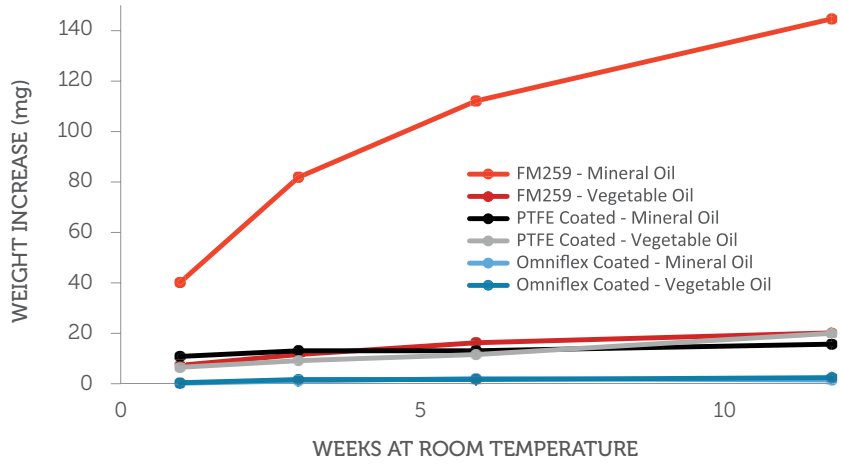

Figure 4: Weight increase as a function of time in contact with oils, for coated and uncoated bromobutyls, as specified in the legend.

All Omniflex-coated products are produced in Datwyler's state-of-the-art manufacturing facility known as FirstLine®. Today, primary packaging component manufacturing is considered to be an extension of the drug manufacturing process itself and the FirstLine® facility was designed to meet the evolving standards of the parenteral industry. The facility design, process flow, gowning protocols, personnel and material flow, and automation all result in the lowest endotoxin, bioburden, particulate, and defect levels available in the industry.

OMNIFLEXCP® PLUNGER DESIGN BY FINITE ELEMENT ANALYSIS

A unique feature of OmniflexCP® is that Finite Element Analysis (FEA) simulations were used to optimise the plunger designs. As seen in Figure 1, the designs for the ISO-standard, 1 mL long plunger (left) and for OmniflexCP® (right) have some slight, but key differences. First, the diameters of the

second and third trailing rills have been slightly decreased as compared with the ISO standard. The other main difference is that the trim edge is undercut on the OmniflexCP® design so that it is no longer in contact with the barrel.

FEA simulations, as in Figure 2, reveal that the compressive stress of the standard 1-3 mL uncoated plunger (left) is highest at the trim edge. Despite the fact that the trim edge is not intended to be a sealing rill, it is the most significant contributor to the frictional forces. In the OmniflexCP® design (right), the trim edge does not come into contact with the barrel surface. This fact, along with the reduced rill diameters in the trailing rills, lead to optimum delivery forces, as discussed below.

These design changes are achieved with no adverse impact on seal integrity. Studies scrutinising the minimum interference fit (combining the lower tolerance for the plunger diameter and the upper tolerance of the barrel inner diameter) showed zero failures of axial compression and dye ingress leak tests.

BARRIER PROPERTIES AND CHEMICAL COMPATIBILITY

Historically, the driver for the adoption of fluoropolymer coated elastomeric closures has been the need for barrier properties. An advantage of the Omniflex spray coating process is that, in contrast to most film coatings, the entire surface of the closure that is in contact with the container walls and drug product, is barrier coated. Indeed, the Omniflex coating is designed both to reduce the number and levels of extractable species from the base rubber, as evidenced in Figure 3.

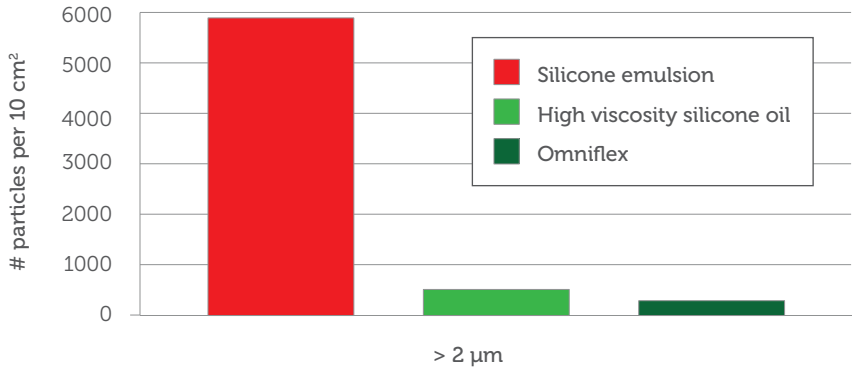

Figure 5: Number of SbVP's (>2µm) per 10 cm² measured according to ISO 8871-3 for a bromobutyl closure siliconised with 350 cSt silicone oil (red), 30,000 cSt silicone oil (light green), and Omniflex coated (dark green).

An important class of leachables that is blocked by the Omniflex barrier coating technology in Figure 3 is metal ions.

In addition to blocking rubber leachables, the Omniflex coating can also prevent the adsorption of certain formulation components and can provide an effective solution to various chemical compatibility challenges. As an example, Omniflex coatings are inherently lipophobic / oleophobic and therefore are an excellent barrier for lipid- and oil-based formulations. Figure 4 shows that uncoated bromobutyl compounds will absorb oils and increase in weight over time which can adversely affect the elastomer's functional performance. On the other hand, the Omniflex coated bromobutyl (in blue) shows close to zero weight increase as a function of contact time with oils.

REDUCED SUBVISIBLE PARTICLE LEVELS IN PRE-FILLED SYRINGES

Low viscosity silicone oils are associated with high levels of SbVPs. Figure 5 shows the number of SbVPs greater than 2 µm in size per 10 cm² of rubber with various types of lubrication including a 350 cSt silicone oil emulsion (red bar), a 30,000 cSt silicone oil (light green bar) and an Omniflex coating (dark green bar). As Figure 5 demonstrates, in terms of SbVP levels, high viscosity silicone oils have a clear advantage over low viscosity oils and the Omniflex coating provides an even further reduction in particle levels.

Figure 6 shows particle levels in three different size ranges for plungers that have been siliconised with 30,000 cSt silicone oil (red bars) *versus* plungers that have been coated with the Omniflex fluoropolymer barrier coating (blue bars). In Figure 6a, levels are expressed as the number of particles per 10 cm² of rubber while Figure 6b expresses the same as the number of particles per drug contact surface area (assumed to be 0.43 cm², or that of a typical 1 mL long plunger.) While switching from a 350 cSt silicone oil to a 30,000 cSt silicone oil results in a nearly 20-fold decrease in SbVP levels, OmniflexCP® provides a further 50% reduction over the high viscosity oil.

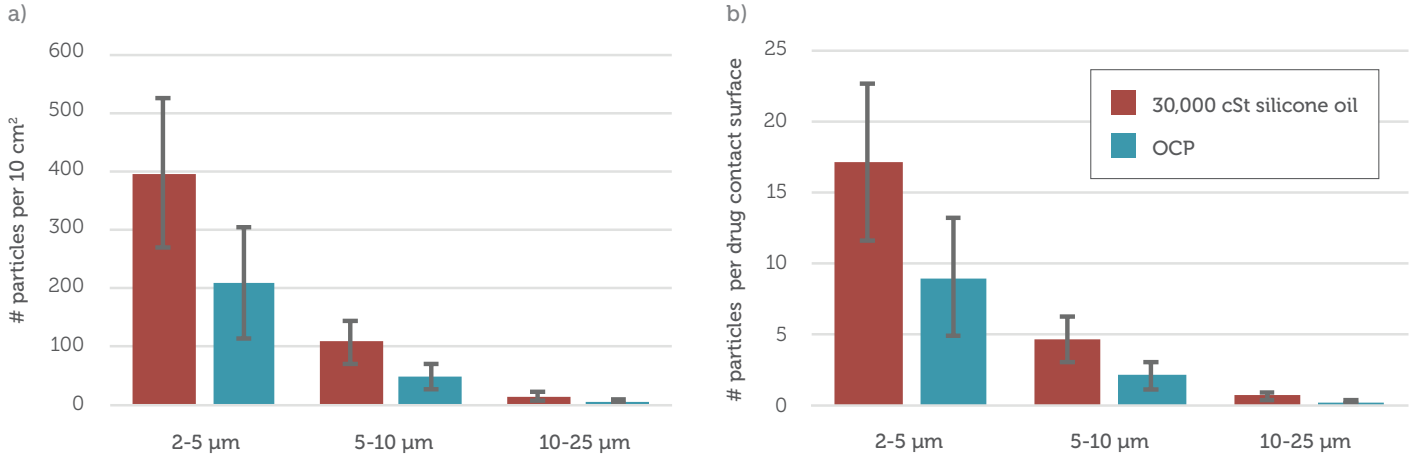

Figure 6: Subvisible particle loads for uncoated, siliconised (30,000 cSt) bromobutyl plungers (red) and OmniflexCP® (blue) (a) normalised to 10 cm² of rubber and (b) per drug contact surface area.

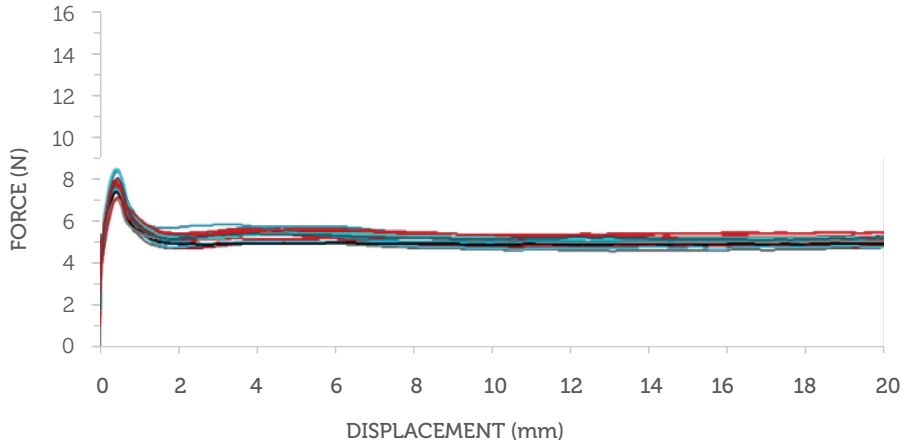

Figure 7: Delivery forces at a rate of 380 mm/min for 20 samples of 1 mL Long OmniflexCP® in WFI-filled glass barrels with baked-on silicone and 27G staked needles, after three days aging at room temperature. (Data courtesy of Gerresheimer.)

The reason for the significant reduction in particle levels with OmniflexCP® is the absence of silicone oil-based SbVPs. This has been demonstrated by the investigations of Felsovalyi et al.[7] In reference 7, the silicone oil-based SbVP levels of OmniflexCP®, a siliconised plunger, and a film-coated plunger were compared. OmniflexCP® was associated with zero silicone oil-based SbVP's while the other two plungers had significant levels detected. In fact, this study showed that when it comes to silicone oil migrating into a prefilled syringe formulation, the plunger was the larger source of free silicone as compared with the barrel – even despite the fact that more silicone oil is applied to the barrel. This is not the case, however, for OmniflexCP® since it is not siliconised.

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CONSISTENT GLIDE FORCES

Due to both the absence of silicone oil and to the optimised mould design, OmniflexCP® has extremely consistent delivery forces from three perspectives: (1) consistent forces as a function of displacement (i.e. no stick-slip behaviour), (2) consistent forces from plunger to plunger, and (3) consistent glide forces with aging.

Figure 7 shows the delivery forces for 20 samples of 1 mL long OmniflexCP®. While delivery forces for any plunger barrel combination can vary widely depending on experimental conditions, there are two important observations that can be made from Figure 7.

First, OmniflexCP®, since it is not siliconised, does not show a stick-slip type phenomenon normally present for siliconised plungers. The glide forces of OmniflexCP® are highly consistent down the length of the barrel. Second, the 20 samples, which have been treated identically in terms of sterilisation, aging, barrel lubrication, etc, yield remarkably consistent delivery forces from plunger to plunger. The standard deviations (RSD) of the break loose and glide forces are 0.4 N (5%) and 0.2 N (4%) respectively. Finally, consistent glide forces with aging of syringes are another advantage of OmniflexCP®. The effect of aging (25°C, 60% RH) on glide forces of 1 mL long plungers is shown in Figure 8 for both ISO-design siliconised plungers (red points) and for OmniflexCP® (blue points). The open squares and dotted lines represent non-sterile parts and the filled squares and solid lines represent steam sterilised plungers.

OmniflexCP® has highly consistent glide forces with aging. The temperature and humidity at which aging studies are performed (refrigerated, room temperature, accelerated aging) have a negligible influence on glide forces for OmniflexCP®.[13]

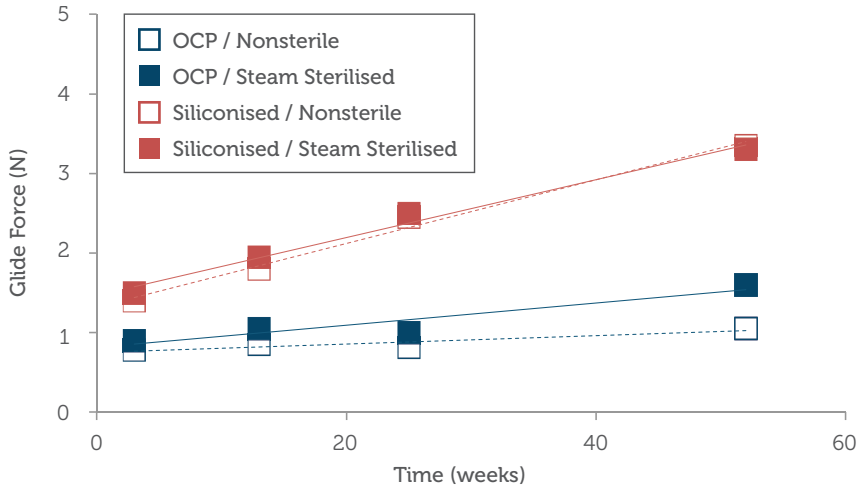

Figure 8: Glide forces for 1 mL long WFI-filled, 27G staked needle, glass syringes as a function of aging time (25°C, 60% RH) with siliconised bromobutyl plungers (red) as compared with OmniflexCP® (blue), before sterilisation (dotted lines, open squares) and after steam sterilisation (121°C / 30 minutes, solid lines, filled squares).

SUMMARY

For coated elastomeric closures, barrier properties alone are no longer enough to meet the needs of biologic drug packaging. Reducing or eliminating silicone oil is being recognised as a means to mitigate risks and reduce time-to-market. No longer is the conventional wisdom always being accepted that the syringe barrel is the predominant source of free silicone oil; instead, the plunger contribution is being more closely scrutinised. OmniflexCP® not only has the advantage of having barrier properties and total coating coverage, it also can eliminate the plunger as a source of silicone oil which significantly reduces SbVP levels in prefilled syringes. Furthermore, the Omniflex coating enables OmniflexCP® to have highly consistent delivery forces.

"No longer is the conventional wisdom always being accepted that the syringe barrel is the predominant source of free silicone oil; instead, the plunger contribution is being more closely scrutinised"

Beyond biologics, OmniflexCP® is finding broad acceptance due to its lack of free silicone oil and consistent forces. Indeed, there are numerous applications outside the scope of biologics for which OmniflexCP® may provide a unique solution including:

- Ophthalmic drugs (where silicone oil droplets must be avoided) [14,15,16]
- Lipid formulations (where oils can otherwise absorb into uncoated rubber)
- Pump delivery applications which require precise dosing (where glide forces must be highly consistent to ensure patient safety)
- Autoinjectors (which require consistent delivery forces)
- Innovative delivery devices novel plunger designs (for which the spray-coating process is well-suited).

OmniflexCP® is a mature technology designed to meet the demands of the biologics industry and beyond and provides an effective solution to a broad range of parenteral packaging needs.

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OmniflexCP®

Coated plungers to meet the highest demands for quality and performance

- NO SILICONIZATION
- ULTRA-LOW SUBVISIBLE PARTICLE LEVELS
- SUPERIOR CHEMICAL COMPATIBILITY
- HIGHLY CONSISTENT DELIVERY FORCES
- DESIGN FLEXIBILITY

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