OmniflexCP®: *Coated plungers to meet the highest demands for quality and performance.*

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In the conservative, data-driven industry of pharmaceutical packaging, market trends clearly indicate a growing demand for fluoropolymer coated elastomeric closures, primarily in order to mitigate risks related to drug stability and compatibility. The Omniflex fluoropolymer coating is highly differentiated from traditional film coatings as it is the first coating to simultaneously provide barrier properties *and* to eliminate the closure as a source of silicone-oil-based subvisible particles. The Omniflex performance advantages are rooted in the coating's chemical composition and its method of application to the elastomer closure. The composition of the coating results in a thin, flexible film with excellent barrier properties and a low coefficient of friction which eliminates the need for siliconization. The tumble-spray coating process enables complete coverage of the article and the ability to readily coat custom designs. As a consequence, 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 subvisible particle levels and highly consistent delivery forces. OmniflexCP® continues to find broad applicability to address a variety of stability, compatibility, and performance challenges, in and beyond the world of therapeutic proteins.

I. INTRODUCTION

Market trends in the parenteral packaging industry indicate a growing preference for fluoropolymer coated elastomeric closures. As the concern and scrutiny over leachables and particulate matter from primary packaging components continue to escalate in the parenteral drug industry, so will the demand for fluoropolymer coated elastomeric closures. Traditionally, the design of film-coated elastomeric closures has focused only on barrier properties. The sole function of the fluoropolymer film coating is to keep rubber leachables out of the drug formulation and to keep formulation components from absorbing into the closure.

Aside from their direct toxicological considerations, leachables can also potentially impact the drug product itself, and, generally speaking, the products that are most sensitive to the presence of rubber leachables are biologics. The efficacy of therapeutic proteins can depend sensitively on the exact chemical make-up and three dimensional conformation of the protein. Interactions with packaging leachables can lead to chemical and/or conformational changes and degradation and/or aggregation, possibly rendering the therapeutic protein ineffective or even immunogenic. Thus, the majority of biologic drug manufacturers do indeed opt for fluoropolymer coated closures.

Probably the most well-known and often cited example highlighting the value of fluoropolymer barrier coatings is that of Eprex® (recombinant human erythropoietin alpha) in pre-filled syringes. In 1998, a number of Eprex® products were formulated using polysorbate 80 as a stabilizer in place of human serum albumin. Not long after those changes, the incidence of antibody-mediated pure red cell aplasia (PRCA) increased substantially in chronic kidney disease patients treated with Eprex® subcutaneous injections.[1] The immunogenic reactions were judged to be most probably caused by organic leachables from uncoated rubber syringe plungers whose levels were increased by the reformulation with polysorbate 80. The rubber leachables were believed to be acting as adjuvants which increased the immunogenicity of Eprex®. As a result, currently all Eprex® pre-filled 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]

With biologics being the fastest growing class of parenteral drugs and with market trends evolving towards higher demands on packaging component cleanliness, fluoropolymer coated elastomeric closures are expected to be adopted at an increasing rate over uncoated rubber closures.

Beyond rubber leachables: Scrutiny over particulate matter in parenteral drugs continues to increase. The increased scrutiny over particulate matter in injectable drugs has been fueled in recent years by regulatory recalls. In 2013, approximately half of the Food and Drug Administration's issued recalls of parenteral products were due to the presence of visible particulate matter.[2] The composition of these particles can vary widely from foreign matter (i.e. glass, brass, or stainless steel) to drug-related particles (i.e. crystallized or aggregated drug product or turbid solutions upon reconstitution).

While larger particulate matter has long been a concern for all parenteral drugs due to the potential for blood vessel occlusion, subvisible particles in therapeutic protein formulations have more recently begun to receive higher levels of regulatory oversight. While much is still unknown about the link between protein aggregates and adverse patient reactions, there is nonetheless significant concern over the potential for protein aggregates to induce immunogenic responses.[3] Since these protein aggregates can be smaller than 2 μm in size, new regulations will continue to intensify the scrutiny around particle detection and characterization. As an example, in August 2014, the FDA issued an industry guidance on immunogenicity assessment for therapeutic proteins. In that guidance the FDA states:

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

Elastomeric closures can contribute to particle levels in parenteral drugs both directly (from silicone oil, particles related to the manufacturing processes and environment, and rubber fragments) 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 have the potential to cause protein aggregation,[5] the above-mentioned guidance appears to support the use of barrier-coated elastomeric closures. However, the increased scrutiny over subvisible particles has implications beyond the scope of controlling rubber leachables.

Barrier properties alone are no longer enough to meet the evolving needs of the biologics industry. While the growth in coated closures has in the past been fueled by the need to reduce leachables from the rubber, this 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 in the biologics industry and beyond.

Traditionally, rubber pre-filled syringe plungers are siliconized with a 350 to 1000 cSt silicone oil for three purposes: (1) to prevent sticking between plungers during shipping and storage, (2) to enable machinability / placement of the plunger into the syringe, and (3) to ensure optimal syringe delivery forces. Even most fluoropolymer film-coated plungers, whose coating only covers the drug contact surface thus leaving bare rubber on the rills, must be siliconized for the three reasons mentioned above.

Although its toxicological profile is generally considered to be safe,[6] silicone oil is known to be one of the most significant contributors to subvisible particle levels in pre-filled syringes.[7] A high level of subvisible particles in biologic drugs can mean additional characterization studies will be required in order to identify the nature of the particles. Since protein aggregation and degradation can potentially present a danger to the patient and diminished efficacy of the drug, the FDA continues to stress the need for characterizing subvisible particles in therapeutic protein formulations:

> *"Assessment should be made of the range and levels of subvisible particles (2-10 microns) 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 and develop*

a mitigation strategy based on that assessment, when appropriate." [4]

Thus, more subvisible particles in a therapeutic protein formulation means more characterization and risk assessment activities will be required.

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

Silicone oil particles can lead to delays in the time-to-market due to the potential for additional characterization and/or formulation work. Furthermore, the interaction of proteins with silicone oil is considered to present a risk to the safety and efficacy of therapeutic proteins. Therefore, with respect to 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 that dramatically reduce silicone-oil-based subvisible particles and provide differentiated compatibility and performance. In the conservative, data-driven industry of parenteral packaging, 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 in pre-filled syringes, was the first coated syringe plunger to not only provide barrier properties but also eliminate the need for plunger siliconization. Today, OmniflexCP® is the best performing fluoropolymer coated plunger technology that addresses the compatibility and performance challenges of the biologics industry and beyond.

II. OMNIFLEX COATING TECHNOLOGY

Omniflex (which is used as 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 main objectives: (1) to be an inert barrier to organic molecules as well as metal ions and bromide ions and (2) to impart a low coefficient of friction and thereby eliminate the need for siliconization. The base rubber formulation used for OmniflexCP® is the Datwyler bromobutyl compound FM257.

The Omniflex coating thickness and uniformity are carefully scrutinized during the product development cycle and in general it is designed to be approximately 20 μm in thickness. Due to the line-of-sight nature of the spray coating process, the entire plunger surface is coated except for the interior of the plunger-rod cavity. This spray coating process is one of the keys to OmniflexCP®'s superior compatibility and performance. The total coverage of the plunger by the Omniflex spray coating is in contrast to the partial coverage of most film-coated plungers and has the added benefit of providing a complete barrier film on top of every rubber surface that is in contact with the syringe barrel or drug product. The total coverage of the lubricious Omniflex coating also eliminates the need for partial siliconization of the plunger rills. Furthermore, the spray-coating process lends itself to easily coating custom designed parts which enables rapid prototyping for innovative drug delivery devices.

The Omniflex coating is applied in a two-step process. In the first step, the plungers are loaded into a stainless steel drum and the proprietary fluoropolymer film is applied by a tumble spray coating process which, in practice, is similar to a tablet coating process. The coated plungers are then subjected to a thermal post-treatment step. This post-treatment process has several intended purposes. First, the elevated temperatures provide sufficient thermal energy to initiate the chemical reaction to covalently bond the coating to the bromobutyl rubber substrate. Second, it has the effect of forming a smooth, continuous fluoropolymer film.

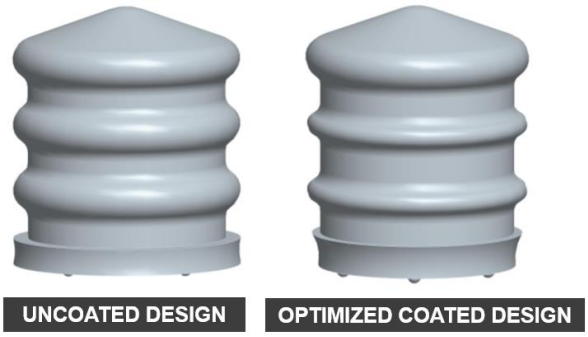


Figure 1. Three dimensional renderings of the 1 mL long uncoated (left) and OmniflexCP® (right) plunger designs.

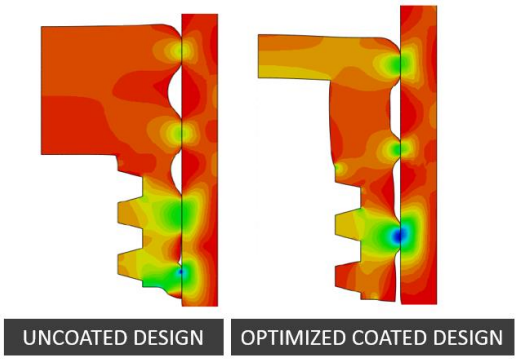


Figure 2. FEA simulations of the compressive stress profiles of the 1-3 mL uncoated (left) and OmniflexCP® (right) plunger designs.

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.

III. OmniflexCP® PLUNGER DESIGN BY FINITE ELEMENT ANALYSIS

A unique feature of OmniflexCP® is that Finite Element Analysis (FEA) simulations were used to optimize the design for both the 1 mL long and 1-3 mL short coated plungers. As can be seen in Fig. 1, the mold designs for the standard ISO-design, 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 to the ISO standard. The other main difference is that the trim edge, located on the bottom of the images, furthest away from the drug contact surface, is undercut on the OmniflexCP® design so that it is no longer in contact with the syringe barrel.

The impact of these design changes is clearly demonstrated in the FEA simulations in Fig. 2. The compressive stress profile of a 1-3 mL plunger in contact with the glass syringe barrel wall shows that the trim edge in the uncoated ISO design (left) is the point of highest stress (and highest contact pressure). Despite the fact that the trim edge is not intended to be a sealing rill, it bears the highest stress and is a significant contributor to the frictional forces. In the OmniflexCP® design (right), the trim edge does not come into contact with the syringe barrel surface. This fact, along with the reduced rill diameters in the trailing rills, lead to optimum break loose and glide forces as will be discussed below.

Studies have demonstrated that these design changes are achieved with no adverse impact on seal integrity. These studies scrutinized the minimum interference fit that could be realized by combining the lower tolerance for the plunger diameter and the upper tolerance of the barrel inner diameter. Under no circumstances did the plunger/barrel combinations fail an axial compression or dye ingress leak test.

IV. BARRIER PROPERTIES AND CHEMICAL COMPATIBILITY

Historically, the primary driver for the adoption of fluoropolymer coated elastomeric closures has been the need for barrier properties. Indeed, the Omniflex coating is designed to both reduce the number and levels of extractable species from the base rubber and also to prevent formulation components from interacting with the elastomer. An advantage of the spray coating application process of Omniflex is that, in contrast to traditional film coatings, the entire

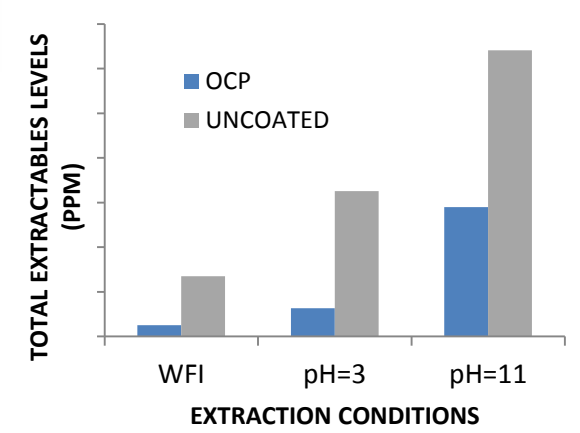


Figure 3. Total relative extractable levels from an uncoated bromobutyl rubber (Datwyler FM257, gray bars) as compared to OmniflexCP® (blue bars) under three different extraction conditions.

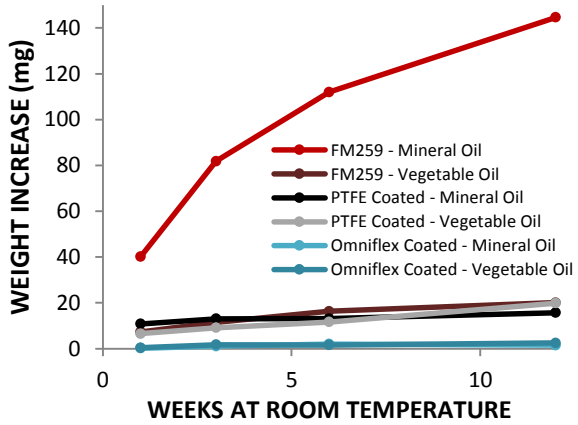


Figure 4. Weight increase as a function of time in contact with oils, for different coated and uncoated bromobutyl rubbers, as specified in the figure legend.

surface of the plunger or stopper that is in contact with the container walls and/or drug product, is barrier coated. The inert Omniflex fluoropolymer coating results in up to an 80% reduction in total extractable levels as evidenced in Fig. 3. An important class of leachables that is blocked by the Omniflex barrier coating technology in Fig. 3 is metal ions. The impact of reduced metal ion leaching from OmniflexCP® on sensitive biologic drugs will be the subject of future studies.

In addition to blocking rubber leachables, the Omniflex coating technology can also prevent the adsorption of certain formulation components and can provide an effective solution to a variety of chemical compatibility challenges. As an example, Omniflex coatings are inherently lipophobic / oleophobic and therefore are an excellent barrier for lipid-based and oil-based formulations. Figure 4 shows that uncoated bromobutyl rubber compounds (in this case, the Datwyler FM259 compound) will absorb oils and increase in weight over time. Especially for pre-filled syringe plungers, this oleophilicity can adversely affect the elastomeric closure'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.

V. OmniflexCP® SIGNIFICANTLY REDUCES SUBVISIBLE PARTICLES IN PRE-FILLED SYRINGES

As mentioned above, traditionally, rubber pre-filled syringe plungers are siliconized with a 350 to 1000 cSt silicone oil in order to prevent sticking, to enable machinability, and to optimize syringe delivery forces. These low viscosity silicone oils are associated with high levels of subvisible particles. Figure 5 shows the number of subvisible particles greater than 2 µm in size per 10 cm^2 of rubber surface area 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 Fig. 5 demonstrates, from the perspective of subvisible particle 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 typical particle levels in three different size ranges for plungers that have been siliconized with a 30,000 cSt silicone oil (red bars) versus

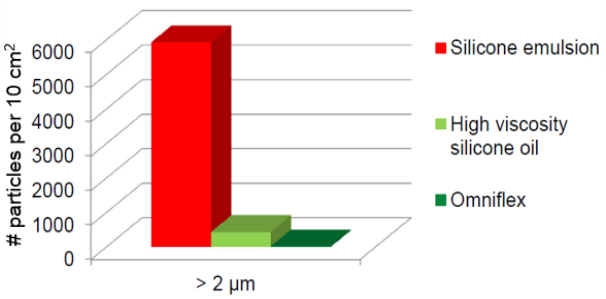


Figure 5. Number of subvisible particles (> 2 µm) per 10 cm² of rubber measured according to ISO 8871-3. The red bar represents a bromobutyl rubber closure siliconized with a 350 cSt silicone oil. The light green bar represents the same article siliconized with a 30,000 cSt silicone oil. The dark green bar represents the same article that has been Omniflex coated.

plungers that have been coated with the Omniflex fluoropolymer barrier coating (blue bars).

In Fig. 6a, levels are expressed as the number of particles per 10 cm² of rubber while Fig. 6b expresses the same data in terms of the number of particles per drug contact surface area which is 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 subvisible particle levels, OmniflexCP® provides a further 50% reduction over the high viscosity oil.

The principle reason for the significant reduction in particle levels with OmniflexCP® as compared to siliconized plungers is the absence of silicone-oil-based subvisible particles from OmniflexCP®. This has been demonstrated by the investigations of Felsovalyi et al.[7] and Fig 7 is adapted from that published work.

Figure 7a shows the silicone oil concentration in various different syringe fill solutions with three different syringe plungers in combination with unsiliconized, bare glass barrels. The far left data on the horizontal axis was collected with OmniflexCP® as compared to a siliconized, uncoated plunger (center, "stopper B") and a film coated plunger (right, "stopper C"). Three different detection methods were compared including atomic absorption (green), HIAC light obscuration (blue), and micro flow imaging (red). The gray bars represent the total amount of silicone oil chemically extracted off the front drug contact surface of the plungers. The figure clearly

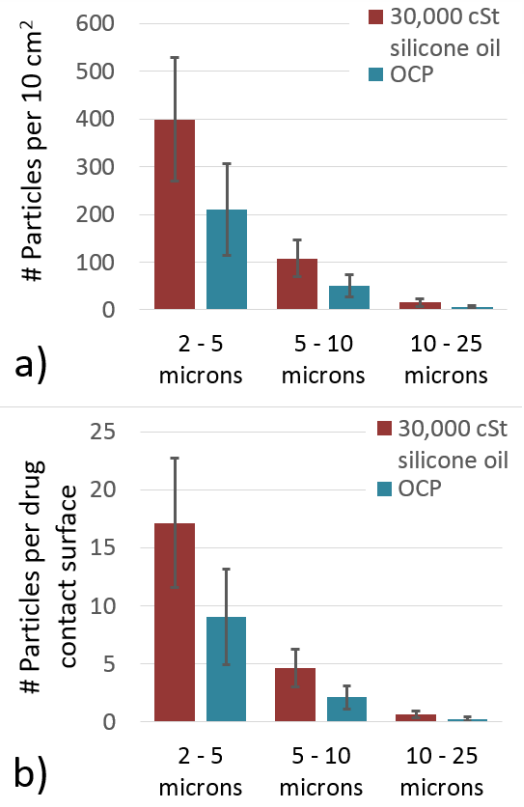
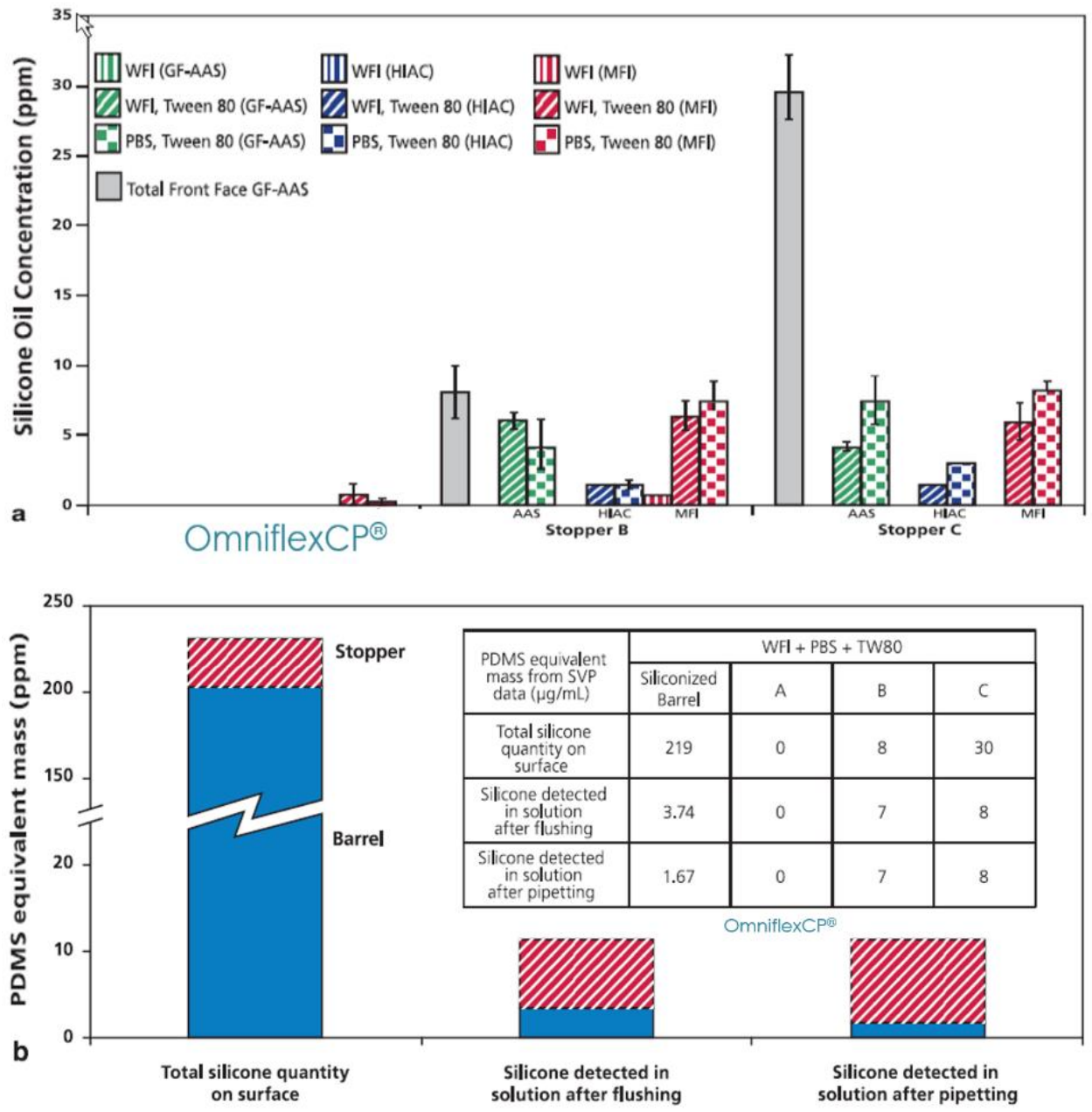


Figure 6. Subvisible particle loads for uncoated, siliconized (30,000 cSt) bromobutyl plungers (red bars) as compared to OmniflexCP® (blue bars) normalized to 10 cm² of rubber (a) and per drug contact surface area (b).

demonstrates that OmniflexCP® has the lowest levels of silicone oil migrating into the syringe solution.

In Fig. 7b, the left bar demonstrates the relative load of silicone oil typically applied to the syringe barrel (blue) versus the syringe plunger (red stripes). As is well-know, significantly more silicone oil is applied to the barrel as compared to most syringe plungers (not including OmniflexCP® where no silicone oil is applied at all). The center and right bars, however, show an interesting contrast. When it comes to the silicone oil that actually migrates into the PFS solution, the syringe plunger is a larger contributor than the syringe barrel – although not in the case of OmniflexCP®. The inset table compares the amount of silicone oil that comes off of OmniflexCP® ("A") versus the siliconized plunger ("B") and the film coated plunger ("C"). Clearly, OmniflexCP® has a distinct advantage – no silicone oil is observed to migrate off.



PDMS equivalent mass from SVP data (µg/mL)	WFI + PBS + TW80			
	Siliconized Barrel	A	B	C
Total silicone quantity on surface	219	0	8	30
Silicone detected in solution after flushing	3.74	0	7	8
Silicone detected in solution after pipetting	1.67	0	7	8

Figure 7. (Figure and caption text are adapted from Ref. 7.) (a) Stopper contributions to various measures of silicone oil concentration. Three different stopper configurations are represented: OmniflexCP® (left), siliconized bromobutyl (middle), and film-coated (right). All three stoppers are assembled in bare glass syringes. The stopper contribution has been evaluated only in flushing mode. The gray bars represent the total silicone oil that migrates into solution from the front face of the stopper measured via solvent extraction. Green measurements represent silicone oil that migrates into WFI (vertical fill), WFI + 0.02% Polysorbate 80 (PS80) (diagonal bars) or PBS + 0.02% PS80 (checkered pattern), measured by AAS. The limit of quantification of the AAS method is 1 µg/mL. (b) Comparison of silicone oil concentration coming from the barrel (blue, solid fill) of a 0.25 mg diving nozzle siliconization process and a film-coated stopper (red, diagonal lines) configuration. Flushing and pipetting data come from SbVP results (MFI) transformed into PDMS equivalent mass. Inset tabulates the concentrations (ppm) for the barrel and three stopper types.

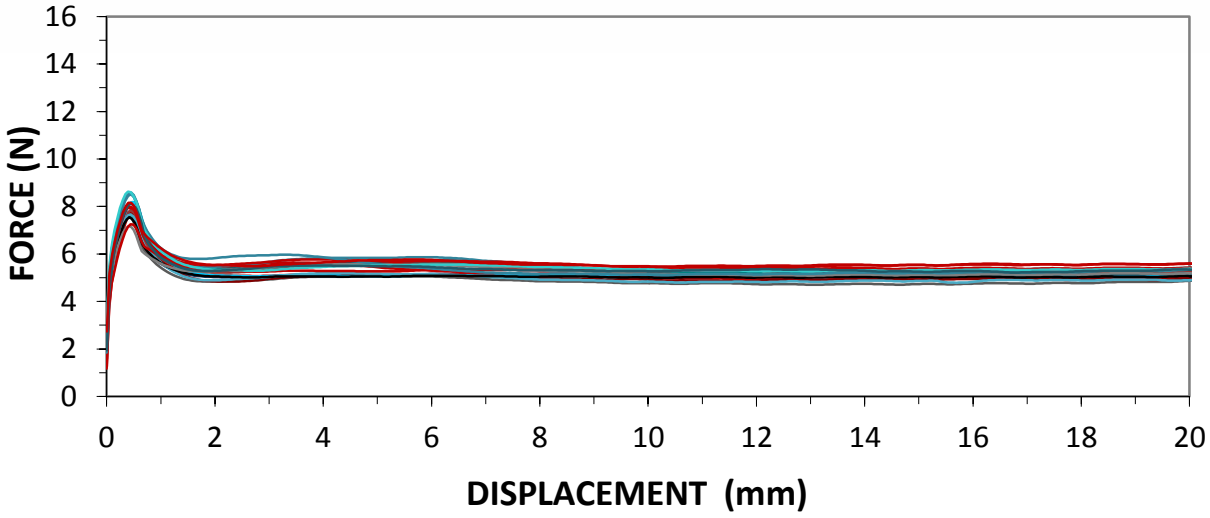


Figure 8. Activation and glide forces at a rate of 380 mm/min for 20 separate samples of 1 mL Long gamma sterilized OmniflexCP® in WFI-filled glass barrels with baked-on silicone and 27G staked needles. Syringes have been aged for three days at room temperature. Data courtesy of Gerresheimer.

VI. CONSISTENT GLIDE FORCES

Due to both the absence of silicone oil and to the optimized mold design, OmniflexCP® has extremely consistent delivery forces from three perspectives: (1) consistent forces as a function of displacement (i.e. no stick-slip type behavior), (2) consistent forces from plunger to plunger, and (3) consistent glide forces with aging. Figure 8 shows the delivery forces for 20 independent samples of 1 mL long OmniflexCP® that have been gamma sterilized and vacuum inserted into glass syringe barrels with baked-on silicone and 27G staked needles. (Note that OmniflexCP® can be placed by either vacuum or vent tube insertion.) Activation and glide forces for any plunger barrel combination can vary widely depending on sterilization conditions, siliconization levels of the barrels, aging time / conditions etc.

There are two important observations that can be made from Fig. 8. First, while it is common for siliconized plungers to experience a stick-slip type behavior which results in glide forces that can oscillate between high and low values, OmniflexCP®, as a result of the absence of silicone oil on the plunger, does not show this type of phenomenon. The glide forces of OmniflexCP® are highly consistent down the length of the glass barrel. In applications where precise dosing is required, consistent delivery forces play a critical role in patient safety.

Second, as observed in in Fig. 8, the 20 samples, which have been treated identically in terms of sterilization, aging, barrel lubrication, etc. yield remarkably consistent delivery forces from plunger to plunger. The standard deviation (relative standard deviation) of the break loose and glide forces over these 20 different samples are 0.4 N (5%) and 0.2 N (4%) respectively.

The activation forces for steam sterilized OmniflexCP® as a function of aging under three different conditions are shown in Fig. 9. Even after accelerated aging for 6 months, the activation forces for steam sterilized OmniflexCP® stay below 10 N.

Finally, consistent glide forces with aging of syringes are another significant advantage of OmniflexCP®. The effects of aging (25°C, 60% relative humidity) on the glide forces of 1 mL long plungers are shown in Fig. 10 for both the ISO design siliconized 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 sterilized plungers. OmniflexCP® has highly consistent glide forces with aging. The temperature and humidity at which aging studies are performed have a negligible influence on glide forces for OmniflexCP®.[13] The trend depicted by the blue lines in Fig. 10 for room temperature aging of OmniflexCP®, looks nearly identical for cold storage and accelerated aging as well (not shown.)

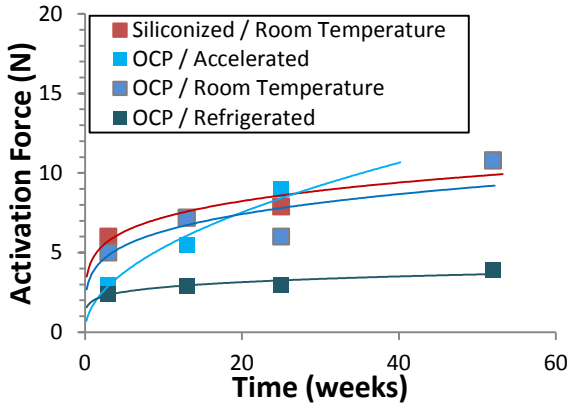


Figure 9. Activation forces for 1 mL long WFI-filled, 27G staked needle, glass syringes as a function of aging time with siliconized bromobutyl plungers (red) as compared to OmniflexCP® (blues) under three different aging conditions: cold storage (4°C), room temperature (25°C, 60% RH) and accelerated aging (40°C, 75% RH) as indicated in the legend. All plungers were steam sterilized at 121°C for 30 minutes. The solid trend lines are meant to aid the eye.

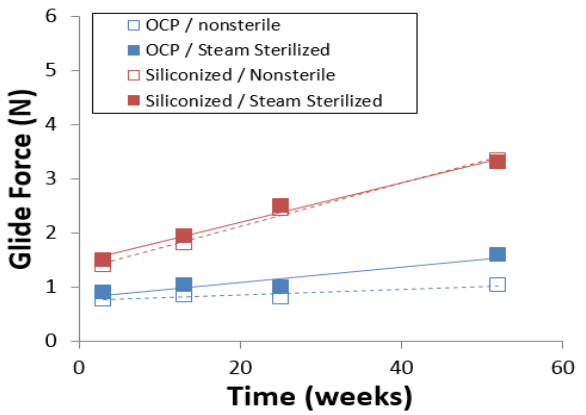


Figure 10. Glide forces for 1 mL long WFI-filled, 27G staked needle, glass syringes as a function of room temperature aging time (25°C, 60% RH) with siliconized bromobutyl plungers (red) as compared to OmniflexCP® (blue), before sterilization (dotted lines, open squares) and after steam sterilization (121°C / 30 minutes, solid lines, filled squares).

VII. 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 recognized 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 scrutinized. OmniflexCP® not only has the advantage of having barrier properties and total coating coverage, it also can eliminate the plunger as a source of free silicone oil which significantly reduces subvisible particle levels in pre-filled syringes. Furthermore, the Omniflex coating technology enables OmniflexCP® to have highly consistent delivery forces which is critical to device performance.

Beyond biologics, OmniflexCP® is finding broad applicability due to its lack of free silicone oil and consistent break loose and glide forces. For example, in some specific applications such as ophthalmic drug delivery, the presence of silicone oil droplets may lead to adverse patient reactions. Studies have shown that low molecular weight components of silicone oil can cause acute ocular toxicity in animal models.[14] Furthermore, the presence of intraocular silicone oil droplets has been detected after some intravitreal injections and these droplets were found to be associated with the use of pre-filled syringes.[15,16] Thus, for ocular injections, there is a need to eliminate silicone oil in pre-filled syringes, regardless of the class of drug molecule.

Indeed, there are numerous other applications outside the scope of biologic drugs for which OmniflexCP® may provide a unique solution including:

- Ophthalmic drugs (where silicone oil droplets must be avoided)
- Lipid or oil-based formulations (where lipids/ oils can 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 which require novel coated plunger designs (for which the spray-coating process is especially 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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