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LUBRICIOUS COATINGS TO REDUCE SILICONE OIL & PARTICLE LEVELS

The market for prefilled syringes continues to grow as does the number of approved biologics delivered in this manner. However, components of the prefilled syringe have the potential to interact with these sensitive drugs rendering them less efficacious or possibly immunogenic. Lubricious coatings that reduce silicone oil droplets and total particle loads may be able to offer a solution to this problem. In this article, Bernd Zeiss from Gerresheimer, and Susan Dounce from Datwyler, outline the results of a study using the combination of a Gx Baked-on RTF® syringe and the OmniflexCP® plunger.

In 2015 more than three billion prefilled syringes (PFS) were sold worldwide, and the market continues to grow. Although anticoagulants and vaccines have dominated in the PFS market, today the number of recombinant proteins stored and administered in prefilled syringes is constantly increasing.

Due to the sensitivity of biologics during storage and the complexity of their mechanisms of action upon administration, primary packaging components used for biologics are faced with the most demanding requirements compared to those used for any other injectable class of drug. The prefilled syringe (including the glass barrel and the elastomeric closure) needs to act as a chemically inert, secure delivery system. The rise of auto injectors and the integration of additional safety features add to the complexity of this syringe system.

For biologics, a major concern is the generation of proteinaceous particles in prefilled syringes. Under certain circumstances, therapeutic proteins can interact with syringe components, in particular the silicone oil that is typically used as a lubricant on both the barrel and plunger. The adsorption/desorption of proteins at aqueous-silicone interfaces can cause non-native structural conformations to arise and protein aggregates to form (Figure 1).[1,2] The nucleation of proteins at silicone-particle interfaces is a known degradation pathway for some biologics and can result in diminished drug efficacy.[3] 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.[4,5]

> "Primary packaging components used for biologics are faced with the most demanding requirements compared to those used for any other injectable class of drug."

The potential risk for protein aggregates to elicit adverse patient reactions has triggered a shift in regulatory requirements related to particles in primary containers. While historically the regulatory focus has been on larger particles which could cause capillary occlusion, new additional scrutiny aims to reduce the immunogenicity risk associated with protein aggregates. It is the expectation of the US FDA that

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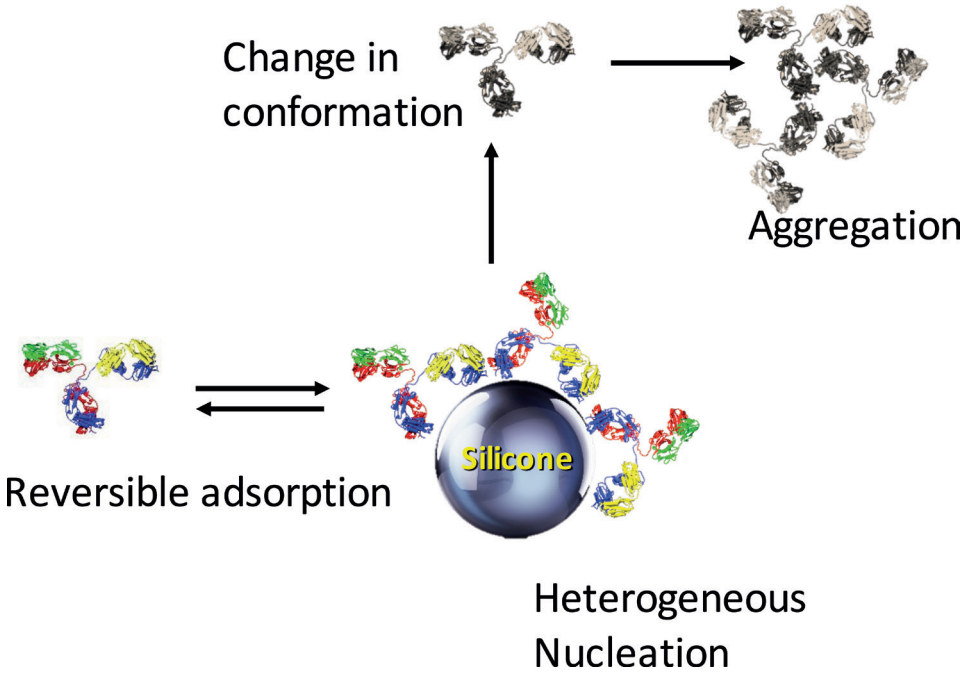

Figure 1: Proteins that are sensitive to silicone oil may undergo heterogeneous nucleation at silicone droplet surfaces or may adsorb / desorb from the droplet which may cause an irreversible change in conformation and an increased risk of protein aggregation.

evidence of a stable production process be provided through measurement and characterisation of particles in therapeutic protein products. Table 1 shows the thresholds for particle levels in therapeutic protein injections (USP<787>), for standard injectables (USP<788> and Pharm Eur 2.9.19), and for ophthalmic solutions (USP <789>). All of these USP and Pharm Eur chapters refer to filled syringes (the combination product). In addition to these pharmacopoeial thresholds for particles ≥10 µm, the FDA Guidance on Immunogenicity Assessment now asks for quantitation and characterisation of particles in the size range of 2-10 µm.

Today, due to the increased scrutiny over particle levels and new regulations around combination products, the manufacturing of primary packaging materials is considered to be an extension of the drug manufacturing process itself. As such, prefilled syringe and elastomeric closures vendors are requested to offer the lowest possible particle loads on the individual components. Both Gerresheimer and Datwyler are addressing these industry needs through innovation in materials, processes and production facilities.

> "Reducing particle loads from syringe plungers is equally as important as reducing particle loads from syringe barrels."

PARTICLE REDUCTION FROM BARRELS AND PLUNGERS

Prefillable syringe manufacturers have found various ways to reduce particle loads. At Gerresheimer this process starts during barrel forming that is controlled by a proprietary camera system, G3, which detects and distinguishes all kinds of both cosmetic and dimensional defects including different types of particles. A dedicated washing process after the barrel forming can already reduce particles from this manufacturing step.

RELEVANT REGULATION		PARTICLE COUNT LIMIT				
		2-10 µm	≥10 µm	≥25 µm	≥50 µm	COMMENTS
USP <787> SbVPs in Therapeutic Protein Injections	**Small volume:** (≤100 mL / container)	N/A	≤6,000 / container	≤600 / container	N/A	Applicable for biologics formulations
						USP <1787>: Orthogonal measurement e.g. MFI recommended
USP <788> Particulate Matter in Injections	**Small volume:** (≤100 mL / container)	N/A	≤600 / container	≤600 / container	N/A	Standard for all injectables
						Measured by light obscuration
USP <789> Particulate Matter in Ophthalmic Solutions		N/A	50 / mL	5 / mL	2 / mL	Measured by light obscuration
FDA Guidance on Immunogenicity Assessment in Therapeutic Protein solutions		Characterisation Only	N/A	N/A	N/A	Particles 2-10 µm to be quantified and characterised

Table 1: Pharmacopoeial and regulatory directives: requirements for particle measurements in filled syringes.

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In the adjacent Ready-To-Fill (RTF®) process, particle loads are again minimised by rinsing, upright transport of the syringes and by avoiding glass-to-glass contact. Above all, the use of the proprietary heat-curing process (baked-on RTF®) is advantageous to reduce the number of silicone-oil-based subvisible particles (SbVPs) migrating from the syringe barrel. This proprietary baked-on lubricious silicone coating is highly uniformly distributed, inert and long lasting. The reduction of particle levels due to the Gx Baked-on RTF® curing process is reflected in the new data of this publication. The Gx Baked-on RTF® syringe in combination with a silicone-free plunger allows very low particle loads to be achieved and the needs of the biologic drug delivery to be met.

Reducing particle loads from syringe plungers is equally as important as reducing particle loads from syringe barrels. At Datwyler, this is accomplished through lubricious barrier Omniflex coatings, which do not require siliconisation, and through state-of-the-art clean manufacturing facilities known as FirstLine®.

Datwyler's Omniflex Coated Plungers (OmniflexCP®) utilise a proprietary, flexible fluoropolymer spray-coating technology that is designed to:

1. Be an inert barrier
2. Impart a low coefficient of friction without siliconisation.

The entire plunger surface is covered (in contrast to the partial coverage of most film coatings) and has the benefits of providing a full barrier and eliminating the need for siliconisation of the plunger ribs. The absence of siliconisation eliminates the largest source of subvisible particles and translates into ultra-low subvisible particle loads from the plunger. All Omniflex-coated products are produced in Datwyler's state-of-the-art manufacturing facilities known as FirstLine®.

FirstLine® facilities are designed and operated under a zero defect philosophy. The process flow, gowning protocols, personnel and material flow, and state-of-the-art automation all result in the lowest endotoxin, bioburden, particulate and defect levels available in the industry.

In the following sections an investigation of the optimisation of lubricious coatings on the syringe barrel and the plunger is presented. The aim of this study was to characterise and significantly reduce the overall particle loads and specifically the silicone oil droplet loads in a prefilled syringe system intended for biologic drug delivery.

The combination of the Gx Baked-on RTF® syringe and the OmniflexCP® plunger (Figure 2) is found to provide particle loads that can meet the new stringent pharmacopoeial requirements for therapeutic protein products.

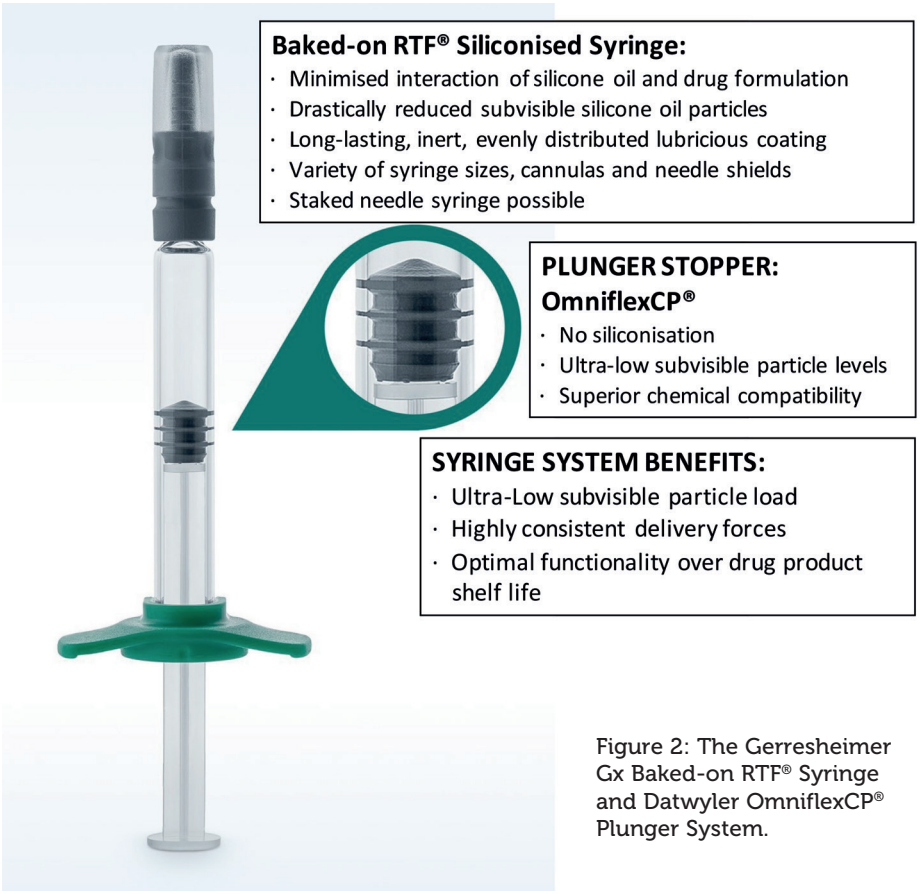

Figure 2: The Gerresheimer Gx Baked-on RTF® Syringe and Datwyler OmniflexCP® Plunger System.

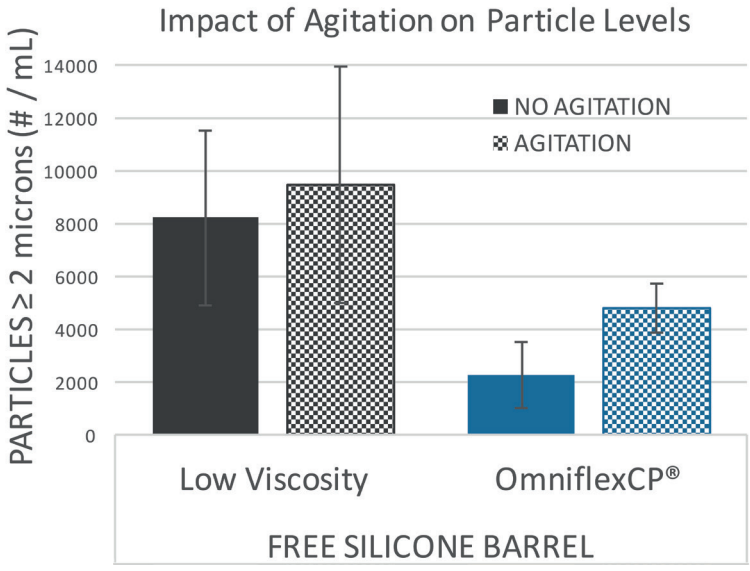

FIGURE 3. The impact of agitation on particle levels in a 1 mL long syringe at the 1 week time point. The syringe barrel has been lubricated with free silicone oil (i.e. not baked-on). The grey bars represent plungers lubricated with low viscosity (350 cSt) silicone oil while the blue bars represent Omniflex-coated (non-siliconised) plungers. Agitation (represented by the checkered bars) was performed for 1 minute on a rotary shaker table at 400 RPM. Particle measurements were made by HIAC Royco light obscuration.

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EXPERIMENTAL METHODS

Sample Preparation

1 mL, long syringes with either free silicone (0.5±0.2 mg/syringe) or baked-on silicone (<0.2 mg/syringe) were filled in ambient conditions with 10 mM phosphate buffered saline containing 1 mg/mL polysorbate 80. Plungers were lubricated (~30 µg/cm²) with either low viscosity silicone (Dow Corning DC360, 350 cSt), high viscosity silicone (Bluestar, 30,000 cSt) or were Omniflex coated (no siliconisation).

For the one-week time point, syringes were aged horizontally under ambient conditions. For the three-month time point, syringes were aged horizontally under accelerated conditions (40°C, 75% relative humidity). Syringes that were agitated were placed onto an orbital shaker table (1 min @ 400 RPM) prior to particle level measurements. Time was allowed after agitation and prior to measurement to allow air bubbles to dissipate.

Particle Level Measurements

Particle levels were measured by HIAC Royco light obscuration and by micro-flow imaging (MFI). Due in part to the ostensible intrinsic limitations of light obscuration to count non-spherical and/or transparent particles, particle levels measured by MFI are higher than those measured by HIAC Royco, though qualitative trends are consistent between the techniques.[6]

In both cases, a blank solution was used to clean the instrument and to ascertain the cleanliness of the sampling vessel. Acceptance criteria for the particle levels of the blank solution must be met prior to sample measurement. The contents of the syringes were dispensed into the clean sampling vessel by actuating the plunger in the forward direction.

In the case of MFI, one measurement was made per 1 mL long syringe. In the case of HIAC Royco, which requires greater sample volume, the contents of 15–20 syringes were pooled together for multiple sequential measurements.

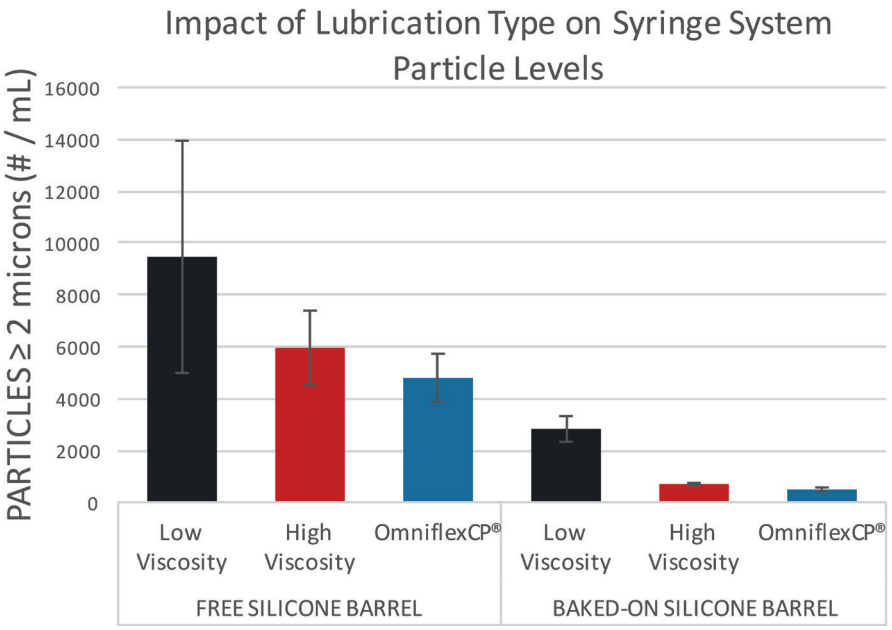

Figure 4: The impact of barrel lubrication type and plunger lubrication type on syringe system particle levels, measured by HIAC Royco light obscuration, after 1 week aging in ambient conditions, with agitation prior to the measurement. The three bars on the left represent a syringe barrel with free silicone while the three bars on the right represent a barrel with baked-on silicone. Grey and red bars show plungers lubricated with low and high viscosity silicone oil respectively. Blue bars represent Omniflex-coated plungers (not siliconised).

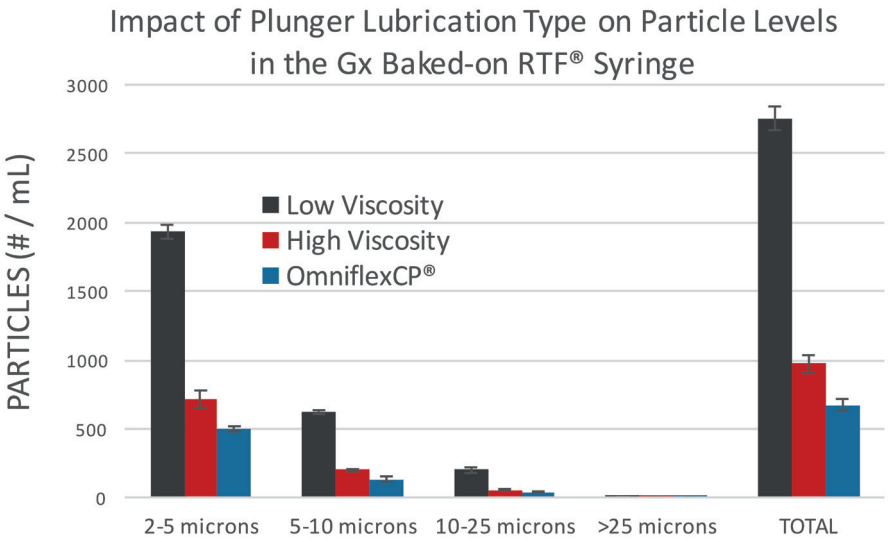

Figure 5: Particle loads by size category as measured by HIAC Royco light obscuration in the Gx Baked-on RTF® syringe with various plungers lubrication types. Syringes were aged for 3 months under accelerated conditions and agitated prior to measurement.

RESULTS

Impact of Agitation

Shaking on a rotary shaker table for one minute prior to sample measurement was intended to mimic the agitation that a prefilled syringe may experience during transport or at the point of care when a patient or healthcare worker handles the syringe and administers the injection. Figure 3 shows the impact of such agitation on the particle levels (≥2 µm) in a free silicone syringe in combination with plungers that are lubricated with low viscosity silicone oil (grey bars) or Omniflex coated (blue bars). The solid bars are samples that have not been agitated while the checkered bars have been agitated. Since a notable increase in particle load is observed with agitation, the data reported hereafter is for agitated samples only.

Impact of Plunger and Barrel Lubrication Type on SbVP Levels

In Figure 4, particle levels (≥2 µm) after one week of ageing in ambient conditions, with agitation prior to testing, were measured by HIAC light obscuration. It is evident that both the barrel lubrication method and the plunger lubrication method impact total particle levels.

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The three bars on the left side (free silicone barrel) show significantly higher particle counts as compared with the baked-on silicone barrel (three bars on the right). Interestingly, even in the case of free silicone on the barrel, the plunger lubrication method significantly impacts the system particle counts with the Omniflex lubricious barrier coating (blue bars) providing the lowest possible level of subvisible particles.

The combination of the Gerresheimer Gx Baked-on RTF® syringe with the Datwyler OmniflexCP® plunger provides a 95% reduction in particle levels over a traditional siliconised barrel/plunger system.

Figure 5 (on previous page) shows a closer examination of the Gx baked-on RTF® syringe in combination with different plunger lubrication systems after three months ageing under accelerated conditions as measured by HIAC Royco light obscuration after agitation. In all cases, total particle levels are dominated by particles <10µm and the highest particle levels are observed for plungers lubricated with low viscosity (350 cSt) silicone oil. In the Gx Baked-on RTF® syringe, OmniflexCP® provides a 75% reduction in particle load *versus* a typical siliconised plunger.

Particle Characterisation and Contributions from Silicone Oil

The use of micro-flow imaging allows the nature of the particles to be further characterised through the use of image analysis and morphological filters. Importantly, silicone-oil-based subvisible particles can be distinguished from other particles.

In Table 2, typical images of silicone oil particles and other transparent and opaque non-spherical particles are shown. The silicone oil droplets have characteristics of being highly circular and dark in colour with a white centre. By applying morphological filters to the particle images, the contribution of silicone oil to subvisible particle levels has been ascertained to a reasonable approximation.

Figure 6 shows the total particle levels, measured by MFI, in a traditional syringe system versus the Gx Baked-on RTF® syringe. The left bar represents a system with free silicone on the syringe barrel and a high viscosity siliconised plunger. The right bar represents the Gx Baked-on RTF® syringe in combination with OmniflexCP®. The blue portion of the bars is the contribution from silicone oil droplets while the grey portions correspond to all other particles.

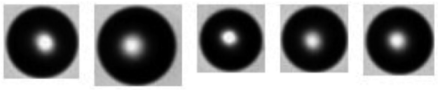
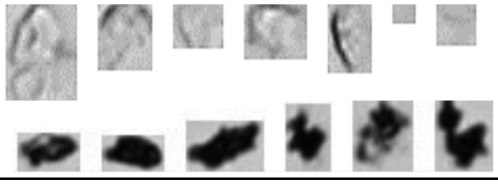
MFI IMAGE ANALYSIS OF PARTICLES IN PREFILLED SYRINGE SOLUTIONS	
SILICONE OIL DROPLETS	
OTHER PARTICLES (i.e. glass, rubber, dust, etc.)	

Table 2: MFI images of silicone oil and non-silicone-oil particles.

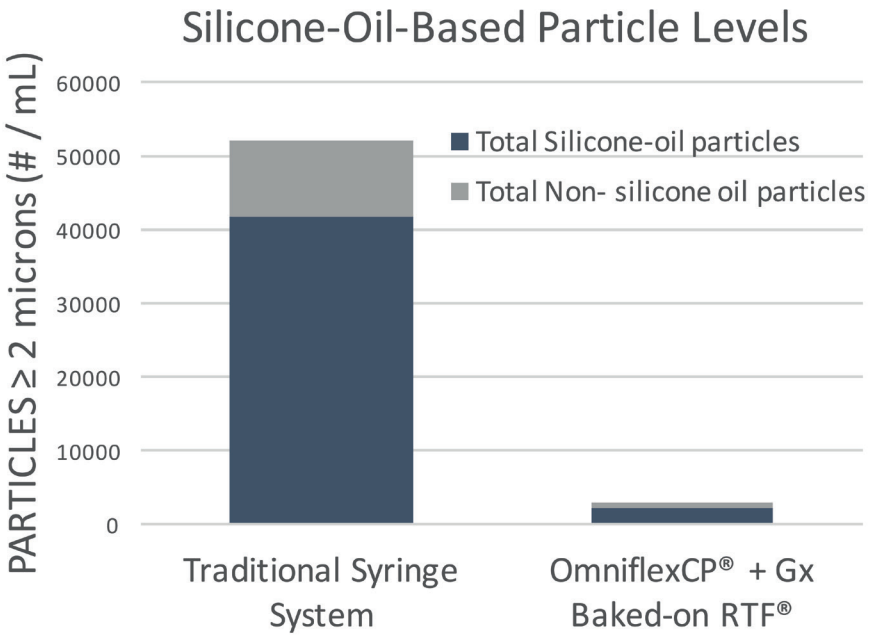


Figure 6: Particle level measurements by MFI in a traditional syringe system (left bar, free silicone on the barrel and a high viscosity siliconised plunger) versus the Gx Baked-on RTF® Syringe with OmniflexCP® (right). Syringes have been aged under accelerated conditions for three months. The blue portion of the bars represent silicone-oil-based particles and the grey portion of the bars represent other particles.

In these MFI measurements made after three months accelerated ageing, the Gx Baked-on RTF® syringe / OmniflexCP® plunger system offers a 95% reduction in particle levels as compared with the traditional syringe system. In the case of the traditional syringe with the high viscosity silicone oil plunger, 80% of the total particle count is due to silicone oil droplets. With the baked-on silicone on the barrel and the lack of free silicone oil migrating from OmniflexCP®, a dramatic reduction in silicone-oil-based particles is realised with the combined Gx baked-on RTF® syringe / OmniflexCP® system.

System Functionality

In addition to the focus on subvisible particles, the overall syringe performance must not be neglected. Low and repeatable break-loose and gliding forces are important syringe features not only for manual PFSs but especially for PFSs used with auto injectors. Although low silicone levels can lead to low particle loads in the syringe, this can conversely lead to higher delivery forces. In a long-term study with different plungers carried out by Gerresheimer, the impact of storage, stoppering method and siliconisation level of Gx RTF® syringes was scrutinised.

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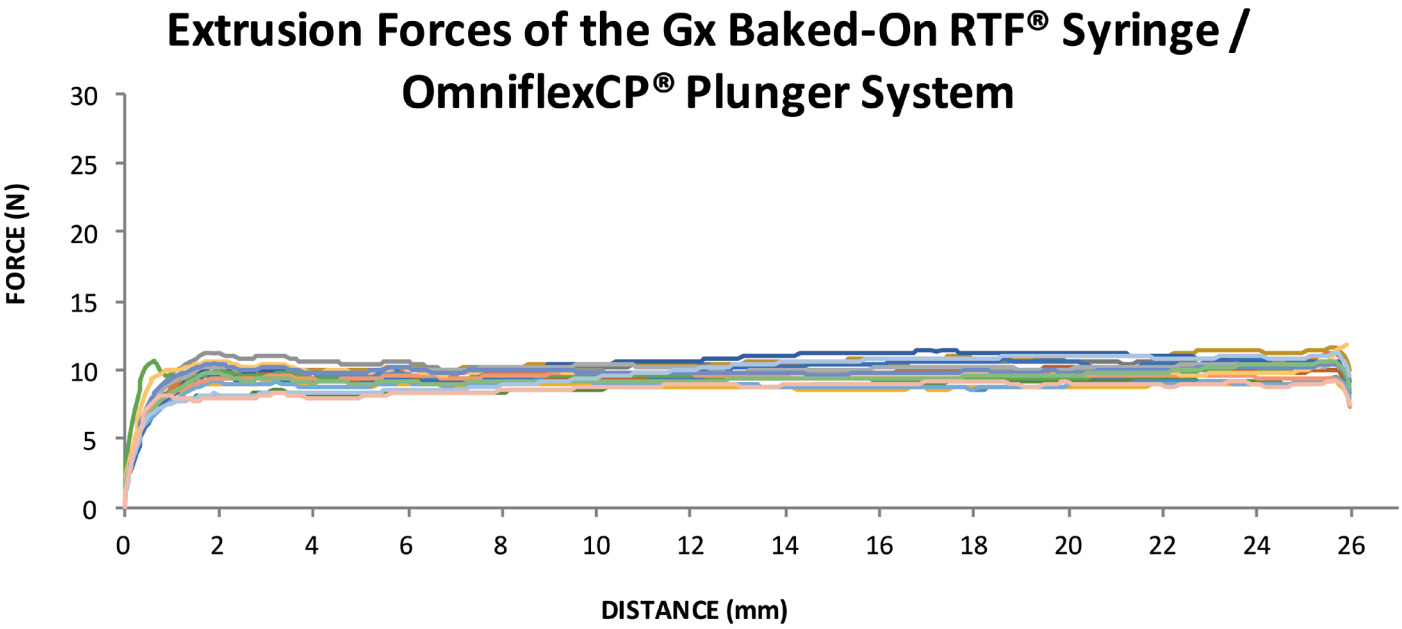

Figure 7: Extrusion forces for the Gx Baked-on RTF® / OmniflexCP® syringe system. The 1 mL, long staked needle syringes (27G) were WFI filled. Plungers were steam sterilised and placed by vacuum placement. The system was aged for one year. Twenty syringe samples were measured at a displacement rate of 380 mm/min..

One of the best results was found with the combination of baked-on siliconised syringes with the OmniflexCP® plunger. Figure 7 shows an extrusion force profile after one year of storage in a 1 mL long baked-on staked needle syringe with OmniflexCP®. Highly consistent delivery forces are observed for this system which makes it ideal for use with auto injectors.

CONCLUSIONS

Since every component's particle levels are significant contributors to the total particle load in a prefilled syringe, a full systems approach is crucial in order to meet the increasingly stringent regulatory expectations for therapeutic proteins. Given the very low particle load and highly consistent delivery forces of the system and the inert fluoropolymer barrier coating on the plunger, the Gx Baked-on RTF® syringe / OmniflexCP® combination is well suited to meet the stringent requirements of biologic drug delivery.

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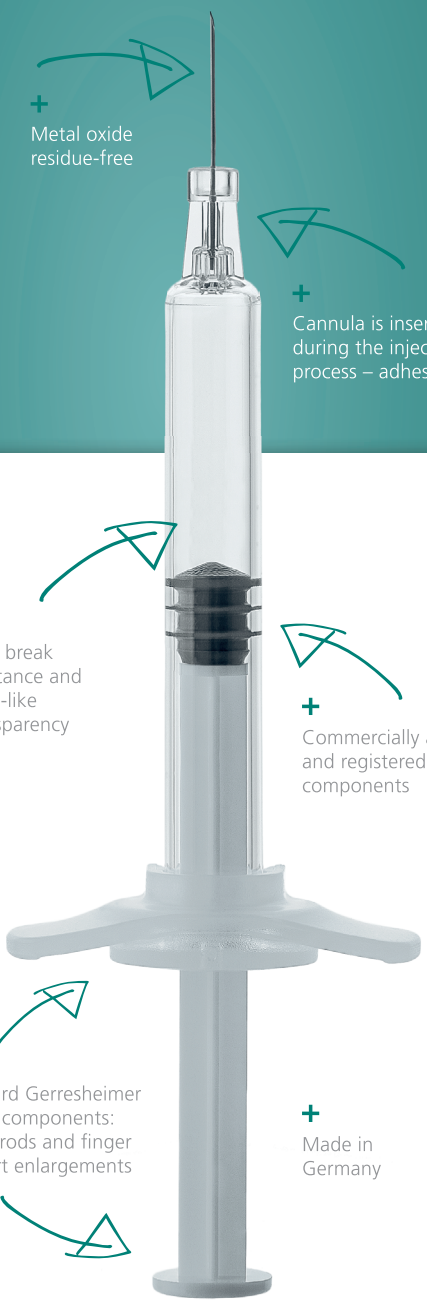

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