Glide into Stability Studies with Bouncer

An extremely useful device for studying the silicone oil coating in prefilled syringes using white light reflectometry and laser interferometry

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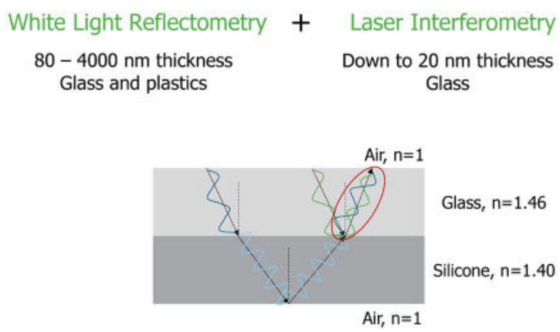
INTRODUCTION

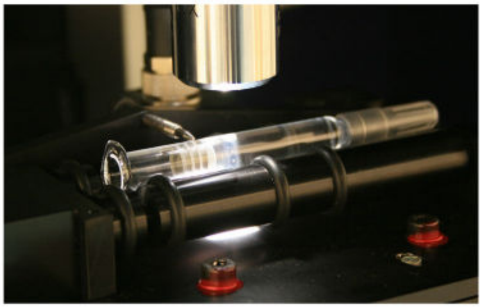
An important trend in chronic care management is the use of manufacturer-prefilled syringes to deliver prescribed drugs. Prefilled syringes (PFS) are sterile, deliver the correct dosage, and improve patient adherence to required treatment with fewer hospital visits. The use of PFS entails fewer steps, which reduces the potential for failure and is more likely to preserve sterility even when used at home.

To make these syringes as foolproof as possible, they are subjected to highly strict quality control protocols. One of the key parameters that must be controlled within narrow limits is the syringe's glide force, which is the force needed to push the plunger to deliver its contents. A low and consistent glide force ensures that the plunger can move smoothly without jamming or stopping up. To achieve this, the syringe barrel is coated with silicone for proper lubrication. The correct amount of silicone, and the uniformity, are critical in this case—too much could cause it to come out into the solution and be injected along with the drug, and too little may not provide sufficient lubrication. It is also critical that the silicone is uniformly distributed throughout the syringe barrel to allow for consistent glide force during the injection.

This article discusses the Bouncer®, an instrument suited to measure the thickness of the silicone coating in a syringe barrel, and the distribution of silicone throughout the barrel. Bouncer uses white light reflectometry and laser interferometry to make these measurements and offers advantages over other types of measuring techniques, as shown in the case studies presented here.

Figure 1: From 20 nm to 4000 nm, inspect syringes from all angles.





MEASURING RANGE AND CAPABILITIES

Using white light reflectometry, it is possible to measure thicknesses as low as 80 nm for silicone coatings on glass and plastic substrates. Measuring thicknesses down to 20 nm on glass substrates requires a laser interferometry method to calculate the thickness (FIGURE 1). Bouncer shines light on the syringe's barrel and measures the light that is reflected back as a result of the difference in refractive index between the air, glass (or plastic), and silicone, at their respective interfaces. The instrument automatically scans from just below the syringe's flange to its tip to gather a "line" of data, then rotates the syringe by a programmed angle and collects another line at the new angle. Bouncer can repeat the process automatically for up to 36 lines, although that granularity is not usually necessary to make an assessment.

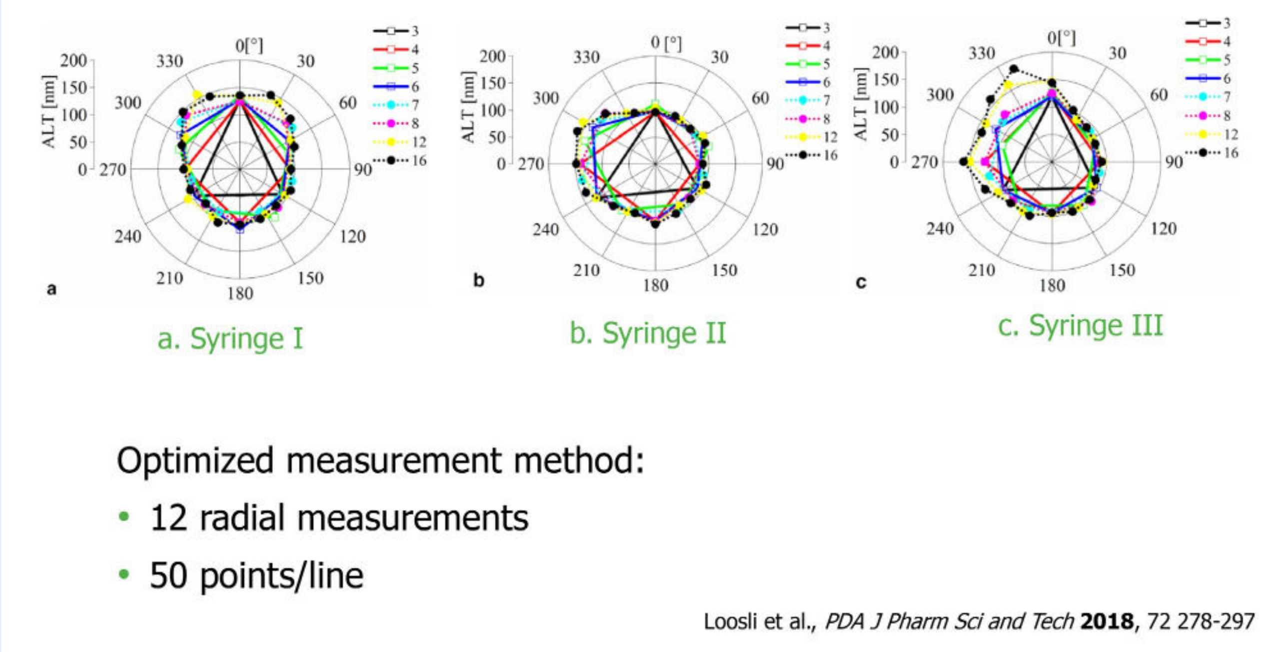
The instrument can accommodate different syringe sizes using three available stages. In general, Bouncer can handle any device that has a cylindrical shape with a diameter of up to 48 mm and length of up to 90 mm. Sample preparation is straightforward—remove the plunger and empty the syringe, then use a vacuum or desiccator to ensure it is dry. It is necessary to always use an uncoated syringe as a control.

Visualizing the silicone distribution is easy, as Bouncer builds two-dimensional plots using the one-dimensional line data as a starting point. Then the instrument superimposes color mapping to clearly show the coating's thickness as a function of the distance from the flange. To fully quantify coating thickness and silicone distribution Bouncer may automatically scan each line twice: first with white light and second with laser light if needed to fill in any datapoints below the white light LOD. Typical measurement times for six lines on a 45-mm long syringe are about five minutes when using white light, and three to four times longer when laser light is needed.

COMPARISON WITH LASER MICROSCOPY

Three-dimensional laser scanning microscopy (3D–LSM) is another technique that can measure silicone coating thickness in syringes. In 2018, Loosli *et al.*[1] published a study comparing the results obtained with this technique with those obtained with Bouncer. The researchers first developed suitable methods for measuring the average coating thickness in sprayed-on syringes. For the Bouncer instrument, they optimized the number of radial lines, the angle of rotation, the measuring length, and the number of measurement points per line. They determined that at least 12 radial measurements of 50 points per line were needed to cover the range of thicknesses encountered in their syringes (FIGURE 2). They reported the average layer

Figure 2: Mapped barrel distribution.



thickness (ALT) for the three certified syringes used in the study, as measured by Bouncer and 3D–LSM. The Bouncer measurements had an accuracy of 90–98%, compared with 96–97% for 3D–LSM, which confirms the Bouncer instrument's suitability for obtaining these measurements.

In addition, the Loosli *et al.* research team gave Bouncer favorable marks for its shorter measurement time per line, its ability to visualize the whole syringe with multiple measurement lines, and the ease of setup for routine measurements. A minor drawback that the researchers noted was the longer setup time to measure baseline values when laser interferometry measurements were required. They also pointed out that this instrument is suitable for both baked and sprayed-on siliconization (homogenous and heterogeneous surfaces, respectively), whereas 3D–LSM is limited to homogeneous surfaces. A major advantage over 3D–LSM is that Bouncer measurements are not destructive to the syringe, while for 3D–LSM, the syringe barrel must be cut in half. This opens up usage of Bouncer to cover storage studies and stability analysis on the same syringe.

FORMULATION STABILITY STUDIES

The ability to carry out drug formulation optimization and stability studies for PFS is another important application for the Bouncer instrument. Some of the formulation components, such as surfactants—as well as the protein concentration levels—can play a key role in their shelf life and stability because they can interact with the silicone oil layer. These studies typically involve testing different surfactant and protein types that are stored at different temperatures over a period of up to three months.

In a recent study, Wang *et al.*[2] at Eli Lilly monitored the glide force in PFS containing two protein formulations (A and B) using two different surfactants at three different protein concentration levels. The surfactants were polysorbate 80 (PS80) and poloxamer 188 (P188). They used a tension compression

Figure 3: PS80 glide force changed.

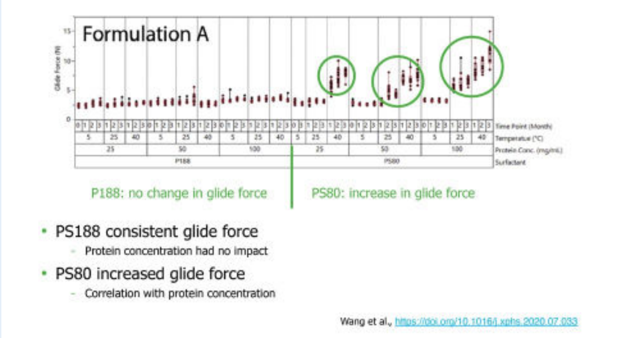


Figure 4: Correlation to siliconization.

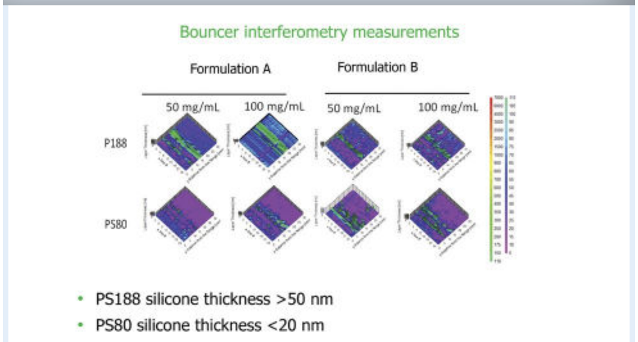
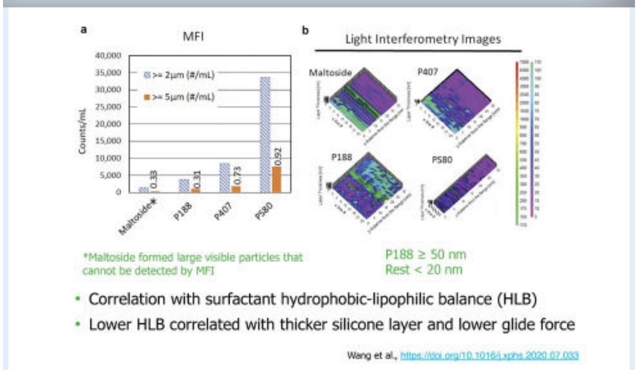


Figure 5: P188 proves to be the best choice.



material test stand to measure the glide force (the force required to eject the contents of the syringe). The researchers also looked for correlations between the glide force and the silicone coating thickness as measured with the Bouncer instrument, and the presence of silicone droplets in the PFS contents using Micro-Flow Imaging (MFI). They found significant changes in the glide force at the highest temperature (40 °C) and high protein concentration even after only one month in formulations containing PS80. In contrast, formulations containing the surfactant P188 were stable under all conditions (FIGURE 3).

To correlate the Formulation A results with the PFS siliconization, Wang's research team obtained a qualitative assessment by imaging the PFS initially, and after three months, at 40 °C using Schlieren imaging technology. These images show that the P188 formulations retain more of the original silicone distribution than those that contained PS80. The Bouncer interferometry measurements, when used to create 2D images, showed that the silicone coating is thicker and more homogeneous in the syringes filled with the P188-based formulations than in those containing PS80 (FIGURE 4). The MFI measurements confirmed that in the PS80 formulations, more of the silicone oil ended up in the solution, as evidenced by the larger number of subvisible particles. Particle formation was more pronounced in formulation A than formulation B, highlighting that the drug also played a role in the result.

In subsequent experiments, researchers tested two other surfactants, maltoside and poloxamer 407 (P407), and found that again P188 gave the best results overall (FIGURE 5). The differences in silicone distribution and coating thickness as measured by Bouncer correlated very well with the glide force measurements. Wang *et al*. were able to demonstrate that the surfactant's hydrophobic-lipophobic balance (HLB) played an important role, as those surfactants with lower HLB correlated with less particle formation and lower gliding forces.

CONCLUSION

The combination of white light reflectometry and laser interferometry used in the Bouncer instrument make it ideally suited for quality control of PFS and for studying formulation stability of the drugs used in these syringes. In addition, Bouncer provides valuable information for method development and formulation screening and characterization of complex formulations. The silicone layer quantification and images generated by Bouncer are highly useful in assessing the homogeneity and durability of the silicone coating on the syringe's barrel, which impacts glide force, a key factor in the syringe's performance.

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REFERENCES

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2. Wang T, Richard C, Dong X, Shi G. 2020, "Impact of Surfactants on the Functionality of Prefilled Syringes." *J. Pharm. Sci*. 109(11):3413-3422