COMPARATIVE PERFORMANCE OF NOVEL SURFACTANT EXCIPIENT AND STANDARD TECHNOLOGIES AT DIFFERENT INTERFACES

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The Background

Many antibody-based drugs and drug candidates have a limited shelf life or will never reach the clinic due to formulation instabilities. One of the root causes preventing drug developers from achieving stable formulations is a lack of ingredients that pair well with biopharmaceuticals in the industry today. As new modalities come out, more tools are needed throughout the manufacturing process, further complicating formulations. In turn, commonly used excipients, such as polysorbates, simply can't provide the stability necessary for antibody-based drugs, leading to material loss, lower yield and shorter shelf life.

FM1000 – derived from inert building blocks – is a new, efficient replacement for problematic polysorbates in biopharmaceutical formulations. In depth research revealed FM1000's immense capabilities to increase yield, lower costs and improve drug stability and quality. Whether formulators are looking to increase the shelf life of their antibody-based drugs or they're simply sick of tossing batches due to formulation instabilities, FM1000 is a promising solution.

The Study

In this study, IFF researchers investigated the novel surfactant, FM1000, to determine its performance at various interfaces when used with antibody-based drugs or drug candidates in comparison to conventional excipients. Monitoring its ability to improve formulation stability, researchers found robust evidence of its superior behavior compared to Polysorbate 80 (PS80), Polysorbate 20 (PS20) and Poloxamer 188. Specifically, FM1000 can address the limitations that basic polysorbates present.

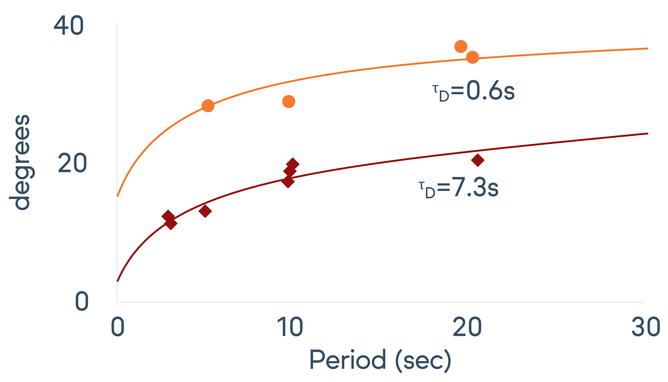
The Method

IFF researchers synthesized the novel surfactant, N-myristoyl phenylalanine polyether amine diamide (FM1000), by sequential amidation of a C14-acyl chloride with phenylalanine. Other surfactants were pharma grade and obtained from commercial sources; immunoglobulin G (IgG) was acquired from MP Biomedical. Each formulation was prepared in saline and tensiometry was performed on a Teclis Tracker. Quartz-crystal microbalance with dissipation (QCM-D) was completed on a QSense analyzer from Biolin scientific. Contact angle was measured on an Ossila goniometer. Surfactant concentrations were quantified via HPLC with CAD detection.

The Results

Researchers found that FM1000 stabilizes the air-water interface 1-2 orders of magnitude faster than its commonly used counterparts, Polysorbate 80, Polysorbate 20 and Poloxamer 188. This led to improved agitation stability of biologic formulations. Follow-up studies using interfacial dilatational rheology at a water-silicone oil interface (silicone oil being a common lubricant in syringes), found that FM1000 diffuses on and off the interface with a characteristic diffusion time of 0.6 seconds compared to 7.3 seconds for PS80. This faster diffusion enables rapid surface coverage and rearrangement in order to prevent protein adsorption, including the silicone droplets that may form in development. Figure 1 shows the phase angle as a function of period during droplet oscillation measurements of the silicone fluid in a saline droplet. The dashed lines are fits to the LVDT model, from which τ_D, the characteristic diffusion constant for the surfactant, can be calculated.

Figure 1:



Using QCM-D, the adsorption and desorption of the surfactant and protein was measured on and off of a silicon dioxide surface. As shown in Figure 2, mass was rinsed from a silicon dioxide surface for solutions of FM1000 and PS80 with and without IgG present. FM1000 and PS80 had comparable adsorbed mass, but upon rinsing, more of the FM1000 was removed from the surface (85%) compared to PS80 (10%). With protein present, 38% of the material was removed with FM1000, compared to only 3% with the PS80.

Figure 2:

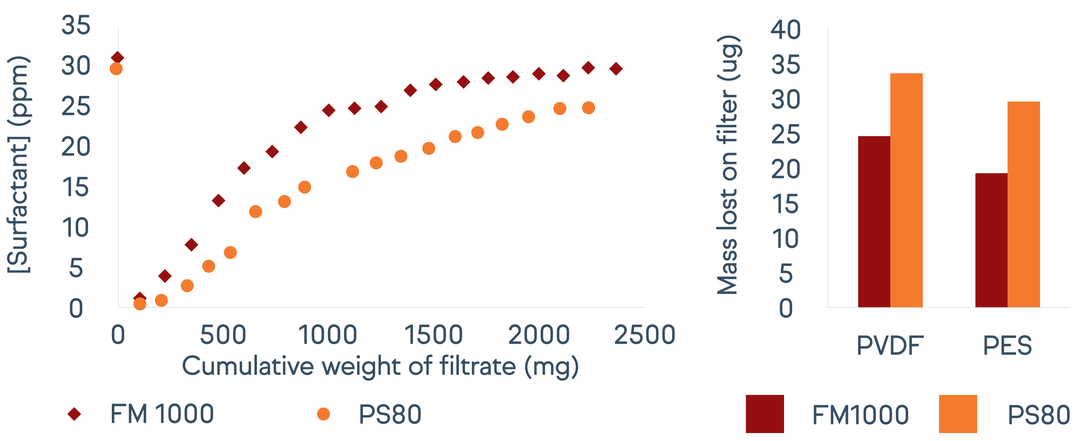
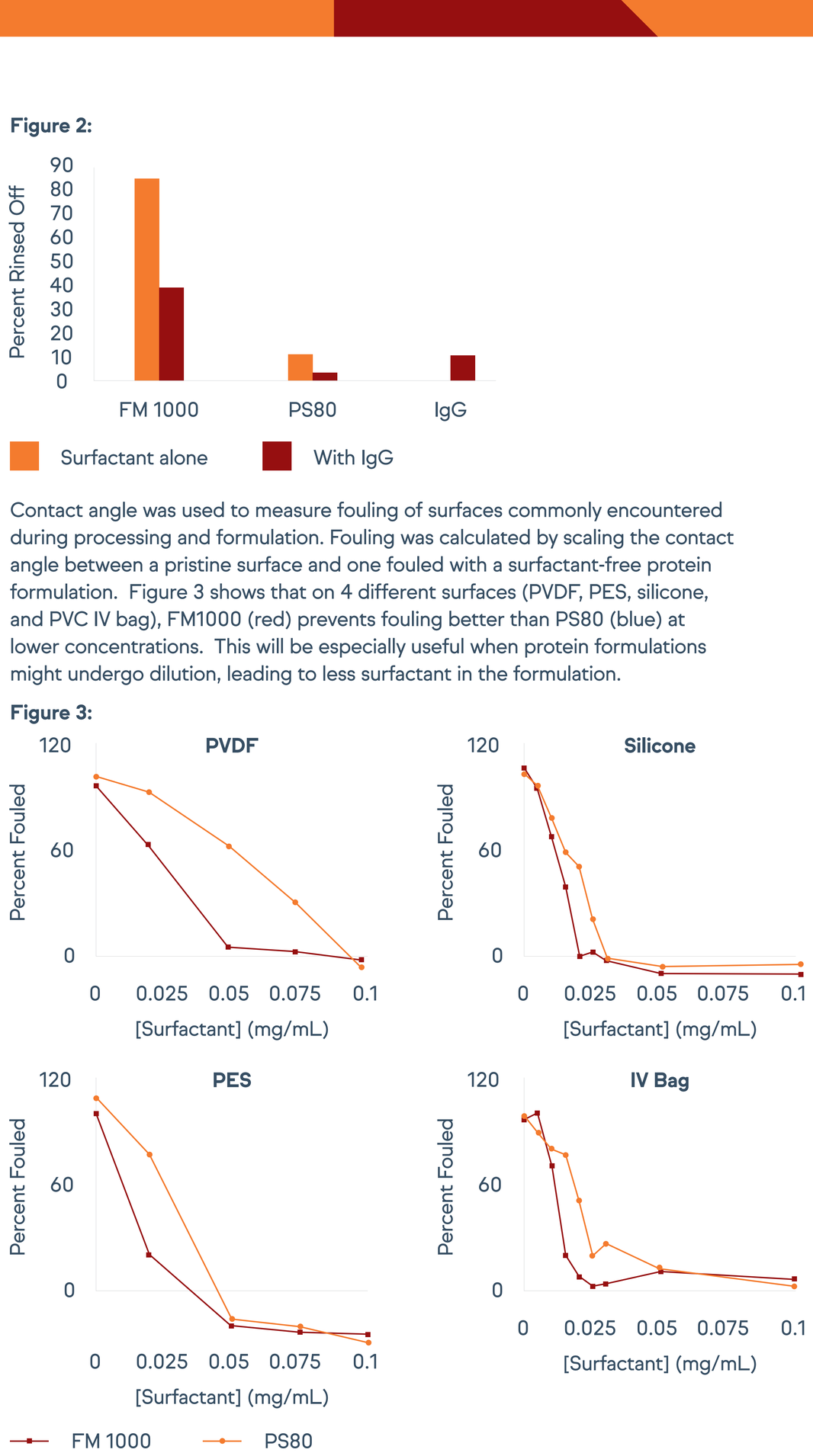


Figure 3:



Contact angle was used to measure fouling of surfaces commonly encountered during processing and formulation. Fouling was calculated by scaling the contact angle between a pristine surface and one fouled with a surfactant-free protein formulation. Figure 3 shows that on 4 different surfaces (PVDF, PES, silicone, and PVC IV bag), FM1000 (red) prevents fouling better than PS80 (blue) at lower concentrations. This will be especially useful when protein formulations might undergo dilution, leading to less surfactant in the formulation.

Surfactant loss on surfaces, specifically sterile filters, was also measured and quantified with HPLC-CAD. Figure 4 shows FM1000 is lost 25-30% less than PS80 on both PVDF and PES filters. FM1000's full recovery is faster than PS80 after 30 ppm surfactants solutions are flown through PVDF and PES filters, as shown in the left plot of Figure 4. Integration of the curves allows for calculation of total mass lost, shown on the right bar graph of Figure 4.

The Conclusion

Throughout the study, researchers consistently concluded that the novel surfactant, FM1000, delivered improved stability and faster diffusion than conventional excipients on several different surfaces. In addition, FM1000 absorbs more quickly and it's more easily reversible from the surfaces. The data in total suggests this novel surfactant not only decreases fouling, but it's also a promising new material for furthering the shelf-life of antibody-derived biopharmaceuticals. Therefore, improved stability of these pharmaceuticals can help to reduce costs and broaden the market for antibody-based drugs, while also lessening the side effects caused by product instability.

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