Hydrophobe Variation in Surfactant Excipient Significantly Impacts Fundamental Performance and Biologic Stability in Liquid Formulation

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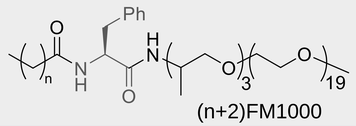
PURPOSE

In recent years, there has been a marked increase in discussions around surfactant mechanisms of biologic stabilization. Many antibody-based drugs and drug candidates have limited shelf life or never reach the clinic due to thermal-mechanical instabilities in formulation, instabilities that can be mitigated by addition of a surfactant. Improving the formulation stability of such pharmaceuticals will reduce costs and broaden markets for those drugs, while also reducing side effects caused by byproducts of instability. This work evaluates the fundamental properties and performance of a rationally-designed and chemically-defined series of surfactant excipients to better understand the mechanisms that drive surfactant stability.

METHODS

N-alkyl phenylalanine Jeffamine M1000 amide molecules (xFM1000 where x=carbons in hydrophobe) were synthesized by sequential amidation of a saturated acyl chloride with phenylalanine followed by amidation of the resulting product with Jeffamine M1000. Comparative surfactants were pharma grade and obtained from commercial sources. NMR and liquid chromatography were used to confirm the identities of the reaction products and purity following xFM1000 synthesis. IgG was acquired from MP Biomedical. All formulations were prepared in dilute buffer or saline. Surface tension was measured on a Teclis Tracker. DLS was performed on a Wyatt DynaPro II.

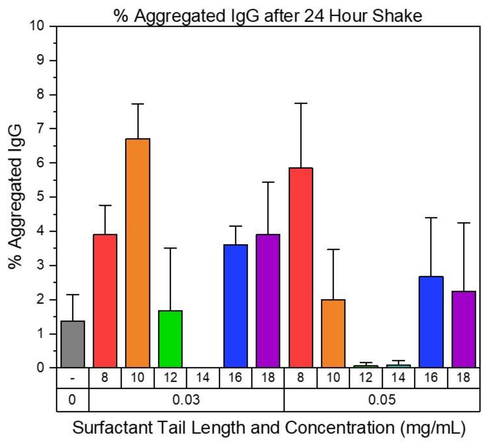
SURFACTANT STRUCTURE



(n+2)FM1000

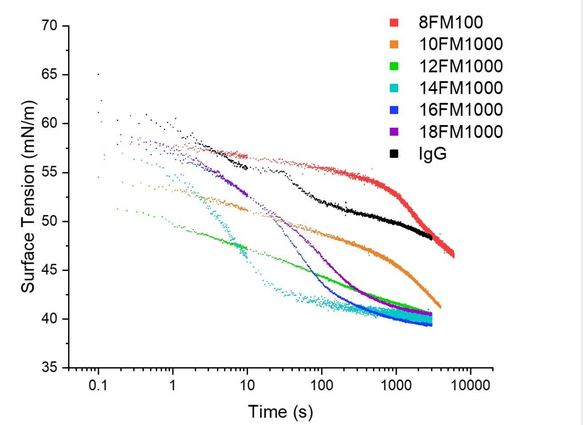
RESULTS

14FM1000 Minimizes IgG Aggregation



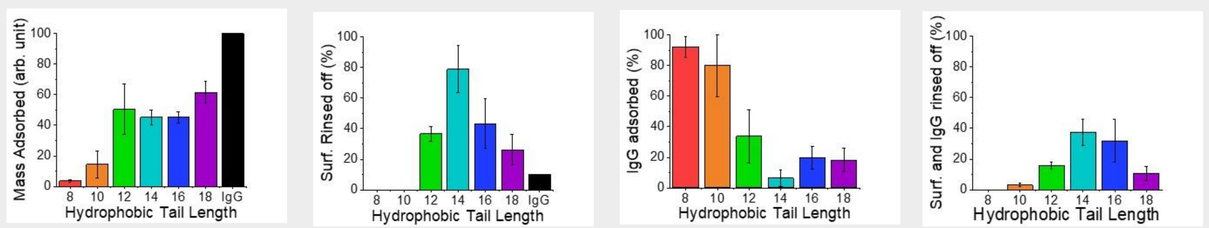
Percent aggregated IgG following a 24 hour reciprocal shake as measured and modeled by DLS. The least amount of aggregate was observed with 14FM1000.

14FM1000 Rapidly Stabilizes the Air-Water Interface



Dynamic surface tension curves for surfactants at air/water interface. 14FM1000 shows the most rapid and highest magnitude drop in surface tension at early times.

14FM1000 is the Most Reversibly Adsorbing and Blocks IgG Adsorption



Quart Crystal Microbalance with Dissipation was used to measure adsorption and desorption of surfactants or surfactants and IgG from a SiO_2 surface in saline. Left two graphs show mass adsorbed (normalized to IgG alone) and percentage of surfactant rinsed off the surface. Right two graphs show percentage of IgG mass adsorbed (compared to IgG without surfactant) and percent of adsorbed mass to rinse off.

CONCLUSIONS

A chemically-defined series of surfactants was developed to test how surfactant chemical structure impacts fundamental performance and stabilization of biologics. 14FM1000, the surfactant we have previously explored, was found to be at a sweet spot for properties and performance differentiation from similar surfactants. The differentiated behavior of derivatives within the series offers opportunities for better understanding mechanisms of aggregation for different proteins and directly mitigating biologic-specific instabilities. The data, in total, suggest that these novel surfactants can be promising new materials for improving the shelf-stability of antibody-derived biopharmaceuticals.

ONGOING WORK

We are continuing to further explore the surface interactions of FM1000 derivatives, gaining understanding of how proteins and surfactants will compete, evaluating applications in both container/closures and processing steps.

Interested in evaluating FM1000 as a developmental material in your formulations? Be in touch! We'd love to hear about your challenges and how we might enable you to have higher throughput processes and more stable formulations.

For more information about DuPont technologies for biologic stabilization, contact Joshua Katz.

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