# Preservative-Induced Micelle Formation of Poloxamer 188

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Multi-injection pharmaceutical products such as insulin require excipients to maintain stability and sterility over long periods of time. Nonionic surfactants are commonly used to prevent protein aggregation and small-molecule preservatives are needed to prevent microbial contamination. Of increasing interest in the pharmaceutical industry is the surfactant poloxamer 188 (P188), an ABA triblock copolymer of poly(ethylene oxide) and poly(propylene oxide). While P188 alone in solution does not aggregate below the critical micelle temperature of 37 °C, the addition of commonly used preservatives can induce aggregation, turbidity, and macroscopic phase separation over time, despite the fact that all individual constituents are well below their respective solubility limits. To understand the molecular mechanism that gives rise to this undesirable aggregation, we have employed a variety of small angle scattering techniques to probe solution structure in mixtures of P188 with the preservatives phenol and benzyl alcohol. In this talk, we will present results of a systematic study of the solution structure of P188/preservative mixtures.
Based on small-angle x-ray scattering (SAXS) of P188/preservative mixtures, an intermediate micelle region exists below the turbidity boundary, which is dictated primarily by phenol concentration[1]. Below this critical phenol concentration, which we refer to as the unimer-micelle transition, all components remain dispersed as unimers in solution, while increasing the phenol concentration well above the unimer-micelle transition leads to the formation of large, unstable aggregates that cause the mixture to become turbid. The unimer-micelle transition and the turbidity boundary—both expressed as concentrations of phenol—are modestly sensitive to P188 concentration and linearly dependent on benzyl alcohol concentration. Other parameters that impact micelle formation and phase behavior, including temperature and isotopic labelling, will also be discussed. Our results provide insight into P188/preservative solution stability that will benefit the development of future pharmaceutical formulations utilizing both P188 and small preservative molecules.

*Reference:*
*{1} Ford, R. R.; et al. Micelle Formation and Phase Separation of Poloxamer 188 and Preservative Molecules in Aqueous Solutions Studied by Small Angle X-Ray Scattering. Journal of Pharmaceutical Sciences.* ***2023****, 112 (3), 731–739. https://doi.org/10.1016/j.xphs.2022.09.019.*