FEEDBACK CONTROL OF PARTICLE MORPHOLOGY ENABLES CONTINUOUS MONOCLONAL ANTIBODY CAPTURE VIA PRECIPITATION

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There is renewed interest in using precipitation for the capture of therapeutic monoclonal antibodies in an integrated continuous downstream process. As monoclonal antibody titers now routinely exceed 5 g/L, bulk separation techniques such as precipitation become more attractive relative to adsorptive separations such as bind-and-elute chromatography. We have previously developed a fully continuous precipitation-based monoclonal antibody capture step (1). We precipitate the monoclonal antibody product directly from harvest cell culture fluid with inexpensive, reversible, and non-denaturing precipitants (zinc chloride and polyethylene glycol) in low-complexity continuous-flow tubular reactors and dewater and wash the precipitates in a fully continuous fashion using inexpensive static mixer/microfiltration module pairs.

In the current work, we utilize in-process microscopy to monitor precipitate particle morphology and automated image analysis to determine particle size distribution. Precipitate particle size distribution behavior is a function of antibody feed concentration, precipitant concentrations, and operating flow rates. We have developed data-driven and kinetic models to describe this behavior. We have identified precipitate particle morphology and particle size distribution characteristics that minimize fouling of the dewatering and washing microfiltration modules, facilitating continuous capture for prolonged durations. We have determined precipitation operating conditions and flow formats that produce precipitate particles with these desired characteristics. We employ feedback control based on real-time, in-process particle morphology and particle size distribution measurements to ensure the continuous generation of precipitate particles with properties that enable consistent, robust microfiltration performance. We have demonstrated operation and closed loop control of the continuous precipitation system with multiple industrial monoclonal antibody feeds.

(1) Li Z et al. Continuous precipitation for monoclonal antibody capture using counter-current washing by microfiltration. Biotechnology Progress. 35(6), e2886 (2019). https://doi.org/10.1002/btpr.2886