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# Design of a Continuous Precipitation Operation for Protein Capture

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Increasing product titers challenge chromatographic separations and play to the strengths of bulk separation techniques such as precipitation and liquid-liquid extraction. Further, bulk separation techniques lend themselves readily to true continuous operation without complex equipment. Here we describe the design of a continuous precipitation process for the capture of monoclonal antibodies from concentrated (~100 g/L) cell culture media. A continuous tubular reactor design with static mixing elements was implemented to ensure that each fluid element experienced the same mixing conditions between target and precipitant streams and the same overall fluid shear rate history. The continuous tubular format also permitted the independent control of the perikinetic and orthokinetic phases of precipitation through the spatially sequential addition of multiple precipitants ( $\text{ZnCl}_2$  and PEG3350). The space-time of the perikinetic precipitation portion of the reactor was determined by the characteristic time-scale of perikinetic aggregation; the space-time of the orthokinetic aggregation portion of the reactor was similarly determined. The Camp number of the process was sufficient to produce a stable particle size distribution. Runs conducted with an industrial partner resulted in yields exceeded 80%, ~2.5x reduction in HCPs, and ~16x reduction in LMW impurities. An added benefit of the precipitation operation was that the dewatered precipitate phase had 90+ days of storage stability at between 2 to 8 °C, permitting the insertion of a hold step if needed. The process scaled readily from 50 L to 1000 L by matching power input per unit volume, producing reproducible particle size distributions, yields and purities: for scale up it is possible to both number up and up-size the hardware; it is also possible to scale the continuous process down for small-scale process development work.