INTEGRATION OF CONTINUOUS PRECIPITATION, CRYSTALLIZATION AND FLOCCULATION OF RECOMBINANT PROTEINS

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Increased titer in biopharmaceutical production requires new strategies for economical processing. Precipitation, crystallization and flocculation are unit operation which overcomes productivity limits of chromatography and membrane technology. General engineering principles how to set up a precipitation, crystallization, or flocculation process for purification of recombinant proteins have shown in the past. The biophysical principles of precipitation by salt, organic solvent and non-ionic polymers will be explained and commonality with crystallization and flocculation discussed and it will be shown how they can be integrated into a continuous process for recovery proteins. Thermodynamic (phase diagrams)and engineering models, and kinetics of precipitation, crystallization, and flocculation (orthokinetic and perikinetic phase, induction time) have been developed for several proteins such as antibodies and interferon gamma. Scale up rules will be explained and how a process can be transferred into a continuous operation; in particular, the concept of fractal dimension (Figure 1) and the Camp number discussed.

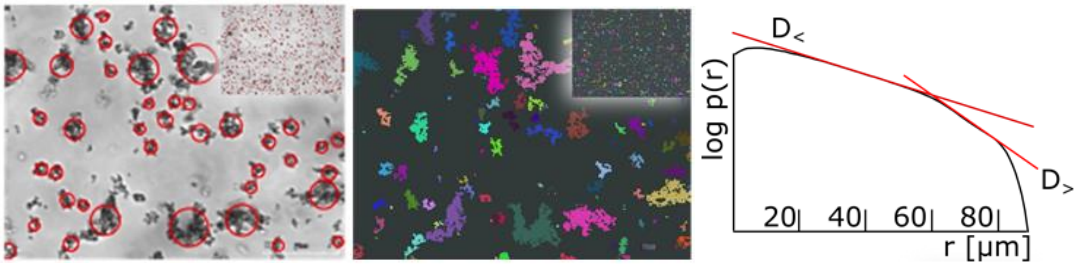

Figure 1 – Determination of fractal dimension of a precipitate

Examples will be shown for products produced in mammalian cell culture and E.coli. A strategy how to implement such process with tubular reactors will be shown and why floc compaction is not desirable when operated in continuous mode. Furthermore it will be discussed if operation at steady state is required.