HIGH CELL DENSITY OPTIMIZATION STRATEGIES FOR CONTINUOUS BIOPROCESSES USING PERFUSION BIOREACTORS

Dr. Jana Mahadevan, Cell culture media development, Process solutions, MilliporeSigma, Saint Louis, MO
jana.mahadevan@milliporesigma.com
Delia Lyons, Cell culture media development, Process solutions, MilliporeSigma, Saint Louis, MO

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Intensified perfusion bioprocesses enable high cell density cultures with higher volumetric productivity and are a promising alternative to the fed-batch technology most commonly used in current biopharmaceutical production processes. Some of the key challenges when working with extremely high cell density cultures are high oxygen demand, consequent generation of shear stress, and foam by spargers, resulting in technical difficulties to maintain the bioprocesses. Our study demonstrates the optimization of bioreactor parameters and culture conditions enable very high cell densities using perfusion systems for intensified processes. One of the parameter focused in our study is to improve bioreactor performance measuring dissolved oxygen (DO) to determine volumetric mass transfer coefficient (kLa) using static gassing out method in EX-CELL® Advanced HD Perfusion Medium to understand the mass transfer as a function of agitation speed and aeration rate using spargers. We evaluated bioreactor process parameters such as agitator speed, gassing rate, properties of the medium, anti-foam agents, surface active solutes that affect kLa to enable higher cell density suspension cultures while maintaining high viability. Our study showed that aeration rate has larger effect on kLa than agitation rate and gives us tool to predict Kla requirements at specific cell densities in the perfusion bioreactor. With the above mentioned optimized kLa conditions, we made improvements on CHOZN®GS cell line for dynamic perfusion (no bleed) bioprocess and showed how changes in the process can enable the increase of cell density by 3-fold, reaching densities above $250x10^6$vc/mL with 2vvd (CSPR<10pL/cell/d) - while maintaining or increasing viability.