OPTIMIZATION AND EVALUATION OF PERFUSION MEDIA IN HIGH CELL DENSITY MAMMALIAN CELL CULTURE SYSTEMS

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Continuous manufacturing has been investigated in both academia and industry as an alternative to batch manufacturing and has been increasingly accepted in the past decade. As a well-recognized method for continuous production of biomolecules expressed in CHO cell culture, perfusion processes are known to have certain advantages over batch and fed-batch processes. The major advantage of perfusion processes is that a favorable environment is provided to cells through the continuous removal of waste by-products and the constant replenishment with fresh media. This environment enables high viable cell densities over long periods of time, resulting in high total productivity. The top candidate (PM8) of a CHO media panel consisting of ten candidates was selected by using several established high-throughput small-scale models and bench-scale bioreactors with the Mini-BioSep acoustic perfusion system, and optimized focusing on factors such as amino acids, vitamins, trace metal elements, and other components through Design of Experiments (DoE) methodology. The perfusion media were further optimized through a multi-step DoE study using a refined high-throughput small-scale model in ambr™15 microbioreactors. In the optimized conditions, the viable cell density peaked at 55 million viable cells per milliliter (vc/mL) and the cell viability was maintained above 90% throughout the duration of the run with a medium exchange strategy of 1 reactor volume per day (RVD) in 11 days cell culture assay. The lead prototype perfusion medium resulted in daily IgG titer that represented an increase of 200% over the titer achieved with a commercially available medium designed for fed-batch culture. The CHO media panel was also evaluated by alpha testers, concluding the same top candidate of the CHO media panel, PM8 in terms of daily peak titers. The viable cell density was achieved over 100 million vc/mL with a cell specific perfusion rate (CSPR) of 22pL/cell/day in a mini-bioreactor with a tangential flow filtration (TFF) system. The volumetric productivity of 3 g/L/day was reached. These media that have been specifically developed and optimized for perfusion applications conducted at a low medium exchange rate will enable perfusion processes to be more efficient and reduce the media cost per gram of antibody produced.