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A CARBON DIOXIDE STRIPPING MODEL FOR MAMMALIAN CELL CULTURE IN MANUFACTURING SCALE BIOREACTORS

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Achieving adequate CO_2 stripping rates in large scale bioreactors is an important consideration during the scale up of animal cell cultures to large scale bioreactors due to the use of relatively low power input and gas sparging rates. It has previously been reported that cell growth, productivity, and product quality attributes such as glycosylation can be significantly impacted when cells are exposed to high CO_2 environments. CO_2 stripping models that depend on the CO_2 mass transfer coefficient have been applied to simulate CO_2 profiles in cell cultures using varied sparger types, reagents for pH adjustment, gas flow rates, and agitation speeds. These models were reported as being validated for a cell culture after cell exponential growth phase. However, in recent years, cell culture processes have been improved to enhance productivity in part through a longer exponential growth phase to achieve higher viable cell densities, making those models less relevant. The current CO_2 stripping models were tested in several improved cell culture processes and resulted in predicted CO_2 profiles not fitting the measured CO_2 profiles. A modified CO_2 stripping model was then developed, of which CO_2 stripping is independent of the CO_2 mass transfer coefficient. Instead, CO_2 stripping is a function of gas flow rates, the residence time of bubbles in the liquid, the time of bubbles being saturated with CO_2, and CO_2 concentrations. The model was validated with two CHO cell culture processes that achieved different peak viable cell density (approximately 7×10^6 cells/mL and 12×10^6 cells/mL) in 25,000-L and 5,000-L manufacturing bioreactors, respectively. The CO_2 stripping model was also applied to optimize cell culture conditions to reduce CO_2 level in cell cultures in the manufacturing scale bioreactors.