Dissolved Carbon Dioxide Determines the Productivity of a Recombinant Hemagglutinin Component of an Influenza Vaccine Produced by Insect Cells

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ABSTRACT

Dissolved carbon dioxide (dCO2) accumulation during cell culture has been recognized as an important parameter that needs to be controlled for successful scale-up of animal cell culture because above a certain concentration there are adverse effects on cell growth performance and protein production. We investigated the effect of accumulation of dCO2 in bioreactor cultures of expresSFþ1 insect cells infected with recombinant baculoviruses expressing recombinant influenza virus hemagglutinins (rHA). Different strategies for bioreactor cultures were used to obtain various ranges of concentrations of dCO2 (<50, 50–100,100–200, and >200mmHg) and to determine their effects on recombinant protein production and cell metabolic activity. We show that the accumulation of dCO2 at levels >100mmHg resulted in reduced metabolic activity, slowed cell growth, prolonged culture viability after infection, and decreased infection kinetics. The reduced rHA yields were not caused by the decrease in the extracellular pH that resulted from dCO2 accumulation, but were most likely due to the effect of dCO2 accumulation in cells. The results obtained here at the 2 L scale have been used for the design of large-scale processes to manufacture the rHA-based recombinant vaccine FlublokTM at the 2500 L scale.