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CO_2 extreme dissolved concentrations influence on growth and CHO cells metabolic characteristics in periodic and continuous processes

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Abstract

The concentration of carbon dioxide dissolved in the medium is one of the key components of mammalian cell culture systems. CO_2 is necessary for the growth and cells development, as well as for maintaining the pH level in the nutrient medium. Non-optimal concentrations of carbon dioxide create a serious problem in the cultivation of cell cultures, including Chinese hamster ovary (CHO) cells, which are the main source of recombinant proteins for therapeutic use. The normal physiological concentration of carbon dioxide for most mammalian cells is 4-8%, which corresponds to a partial pressure of carbon dioxide (pCO_2) about 30-55 mm Hg. The deviations from this interval can slow the growth of cell cultures; significantly rearrange their metabolism, reducing the viability and productivity of cells.

In this paper, the effect of extreme concentrations of dissolved carbon dioxide on the growth of CHO cells in both periodic and continuous processes is elucidated.

When cultivating cells in the fed-batch mode, increasing the CO_2 concentration from 5 to 20% significantly inhibits the growth of the culture, while its reduction to 1% alters the metabolism of cells, blocking the phase of lactate utilization. However, it was found that the cell culture is sensitive to CO_2-stress only at an early stage of cultivation and acquires relative stability already in the period of the late exponential phase of growth.

Similar regularities were observed in continuous (perfusion) processes, when in the early stages of culture growth low values of pCO_2 (1%) led to a strong disruption of lactate metabolism. As a result, intensive accumulation of lactic acid in the nutrient medium was observed, as a result of which the viability and productivity of the crop sharply decreased. In the initial period of cultivation, as long as the concentration of cells is not yet so high that they can saturate the environment with autogenic CO_2, it is necessary first of all to organize an uninterrupted supply of carbon dioxide, not allowing it to blow out from the environment, which is relevant not only for industrial, but also for laboratory reactors.

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