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Enhanced oxygen delivery to a multiphase continuous bioreactor

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HIGHLIGHTS

- A rotating perfusion reactor with spiroid improves oxygen mass transfer.
- The mechanism was based on increasing the interfacial surface between gas and liquid.
- Oxygen saturation was two times faster with the spiroid.

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ABSTRACT

This research investigates a novel continuous bioreactor with significant improvement in gas-liquid transport phenomena. This bioreactor is an automated, horizontally-rotating bioreactor consisting of an outer cylindrical shell and a core with adjustable rotating velocities operated in continuous mode. The under-filled bioreactor provides a multiphase environment for the cell line beneficial for improving the gas-liquid transport phenomena. A spiroid tube is embedded in the inner surface of the outer wall of the bioreactor to increase gas-liquid contact area and thus improve oxygen transfer. Computational fluid dynamics simulations were performed to determine the optimum operating conditions for oxygen transfer. The oxygen transfer rates were determined experimentally, and the related volumetric mass transfer coefficients (k_La) were predicted by mathematical models at a variety of operating conditions. The results indicate that the reactor with the spiroid reached saturation approximately two times faster than without the spiroid.

1. Introduction

Bioreactors have the potential to be applied in large-scale industrial processes to increase productivity. Bioreactors can be simply defined as devices that simulate or provide the most favorable conditions for specific cell lines. Various bioreactors (e. g. bubble columns, agitated reactors, roller bottles, membrane bioreactors) have been applied in the engineering and industrial production. Biological and biochemical experiments conducted in specific devices are controlled under a range of operating conditions in order to seek an optimal method to produce pharmaceuticals (e. g. antibodies, hormones, viral vaccines), solve environmental issues (e. g. wastewater treatment), process food, provide energy source (e. g. conversion of corns to alcohol) and supply cells and tissues lines (Martin et al., 2004).

In many biological cell cultivations, shear stress and oxygen transport of the bioreactor are normally considered to be two of the most limiting factors for the production results. Shear forces are known to have influences on cell shape and membrane structure, which in turn affect the physiology (e. g. metabolism of cells, protein synthesis, DNA and RNA mechanisms) (Abu-Reesh and Kargi, 1989; Ben-Ze'ev et al., 1980; Dewey et al., 1981; Farmer et al., 1978; Folkman and Moscona, 1978; Stathopoulos and Hellums, 1985). The sensitivity of cells to shear stress may vary with the stage of growth, the cultivation culture, and operation conditions (Petersen et al., 1988). To inhibit the activation of human cervical carcinoma HeLaS3 and mouse abdominal fibroblast L929 in the environment of turbulent flow through stainless steel capillaries, Augenstein et al. (1971) concluded that the average wall shear stress of $(0.1–2.0) \times 10^3$ N m^{-2} should be achieved. Leukocytes could be sheared away from the vascular endothelium by shear stress at a range of 26.5 and 106 N m^{-2} in the rabbit omentum (Schmid-Schoenbein et al., 1975). McQueen et al. (1987) observed that a threshold average wall shear stress of 180 N m^{-2} would commence the lysis of suspended mouse myeloma line in turbulent capillary flow. The biochemical response of human T cells to the lectin phytohemagglutinin-P (PHA-P)

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Nomenclature

c_{L0}	initial dissolved oxygen concentration in liquid phase, mol L^{-1}
c_L	dissolved oxygen concentration in liquid phase (water), mol L^{-1}
c_L^*	saturated oxygen concentration in liquid phase at certain temperature, mol L^{-1}
c_f	final dissolved oxygen concentration in the bioreactor, mol L^{-1}
c_{in}	dissolved oxygen concentration entering spiroid loop, mol L^{-1}
c_{out}	dissolved oxygen concentration exiting from spiroid, mol L^{-1}
C_1	constant, $C_1 = max\left[0.43, \frac{\eta}{\eta+5}\right]$
$C_{1\varepsilon}$	constant, 1.44
C_2	constant, 1.9
$C_{3\varepsilon}$	constant, $C_{3\varepsilon} = \tanh\left\|\frac{v_{//}}{v_{\perp}}\right\|$
F_{Nk}	force per unit volume which exerts on the inclusion, N m^{-3}
$F_{O_2,In}$	molar flow rate into the spiroid tube, mol s^{-1}
$F_{O_2,Out}$	molar flow rate out of the spiroid tube, mol s^{-1}
g	gravitational acceleration, m s^{-2}
g_i	ith direction component of the gravitational vector, m s^{-2}
G_b	generation term due to the buoyancy, $G_b = \beta g_i \frac{\mu_t \partial T}{Pr_t \partial x_i}$ or $G_b = -g_i \frac{\mu_t \partial \rho}{\rho Pr_t \partial x_i}$ (for idea gases), J·(s^{-1} m^{-3}) or kg·(m^{-1} s^{-3})
G_k	generation term due to the mean velocity gradients, $G_k = -\rho \overline{v_i' v_j'} \frac{\partial v_j}{\partial x_i}$ or $G_k = \mu_t S^2$ (Boussinesq hypothesis), J·(s^{-1} m^{-3}) or kg·(m^{-1} s^{-3})
I_N	mass interaction term, kg·(m^{-3} s^{-1})
k	turbulence kinetic energy per unit mass, J kg^{-1} or m^2 s^{-2}
k_La	volumetric gas-liquid mass transfer coefficient, s^{-1}
k_La_C	volumetric gas-liquid mass transfer coefficient in bioreactor chamber, s^{-1}
k_La_{sp}	volumetric gas-liquid mass transfer coefficient in spiroid loop, s^{-1}
RPM	rotational velocity of the reactor, round per minute
S_{ij}	mean strain rate, $S_{ij} = \frac{1}{2}\left(\frac{\partial v_j}{\partial x_i} + \frac{\partial v_i}{\partial x_j}\right)$, s^{-1}
S_k	user-defined source term, J (s^{-1} m^{-3}) or kg·(m^{-1} s^{-3})
S_ε	user-defined source term, J (s^{-1} m^{-3}) or kg·(m^{-1} s^{-3})
t	time, s
v	volumetric flow rate through spiroid loop, L s^{-1}
$v_{//}$	component of flow velocity parallel to the gravitational vector, m s^{-1}
$v_\perp$	component of flow velocity perpendicular to the gravitational vector, m s^{-1}
$\vec{v}_N$	velocity vector of phase N, m s^{-1}
V_r	liquid volume of bioreactor, m^3
V_{sp}	liquid volume of spiroid tube, m^3
Y_M	effects from the fluctuating dilatation in the compressible turbulence on the overall dissipation rate, $Y_M = 2\rho\varepsilon M_t^2$, J·($s^{-1}$ m^{-3}) or kg·(m^{-1} s^{-3})

Greek letters

α_N	volume fraction of phase N, percent
δ_N	constant, 0 for the disperse phase and 1 for the continuous phase
ε	dissipation rate, m^2 s^{-3}
η	constant, $\eta = S\frac{k}{\varepsilon}$
μ	molecular dynamic viscosity, Pa s
μ_t	turbulent or eddy viscosity, Pa s
ν	kinematic viscosity, m^2 s^{-1}
ρ_N	density of phase N, kg m^{-3}
σ_k	turbulent Prandtl number for k, $\sigma_k = 1.0$
σ_ε	turbulent Prandtl number for ε, $\sigma_\varepsilon = 1.2$
τ_{ki}	shear stress, Pa

Subscripts

i, j, k	three directions (x, y, z axis) separately

would be affected when the shear stress was 10–20 N m^{-2} over 10 min (Chittur et al., 1988). For erythrocytes in tube flow (three mm tube and whole blood), hemolysis would occur in the entrance with the shear stress of 4000 N m^{-2} (Blackshear and Blackshear, 1987), which was in agreement with the conclusion from Bernstein et al. (1967) that the critical shear stress for the lysis of erythrocytes in turbulent jet was measure as 6000 N m^{-2} for brief exposures (around 10^{-5} s). For hybridoma cells sheared in a coaxial cylinder Searle viscometer, a shear stress level of over 5 Pa in the turbulent regime would damage cells over 0.75 h exposure (Abu-Reesh and Kargi, 1989). A rapid decrease in cytosolic pH of rat aortic endothelial cells cultured in glass capillary tubes resulted from laminar shear stress (1.34 N m^{-2} of shear stress led to the maximal effect 0.09 pH unit) (Ziegelstein et al., 1992). The existence of shear stress cannot be avoided in most bioreactors. Generally, the damage of shear stress resulting from turbulent flow is more severe than that from laminar flow (Chisti, 2001). Thus, a bioreactor with low shear stress is desired in cell cultivation.

Oxygen transfer is one of the most important factors for aerobic bioprocesses. Aerobic bioprocesses normally take place in the aqueous phase where the oxygen solubility could be low due to ionic salts and nutrients (Suresh et al., 2009). However, the consumption rate of oxygen for cells is generally high. Hence, the growth of almost any microorganisms is limited to the amount of oxygen transferred. An increase of amount of dissolved oxygen will result in the increase of secondary metabolites of cells, while the limited oxygen will lead to the decrease of metabolic rate (Vardar and Lilly, 1982). Oxygen transfer rate may be influenced by various parameters including the physical properties of gas and liquid, operational conditions, choice of bioreactor and presence of biomass (Garcia-Ochoa and Gomez, 2009). Many innovative methods have been used to improve the amount of dissolved oxygen, including the use of various bioreactors (e. g. stirred reactor, bubble column, shaking flasks (Maier et al., 2004, 2001), gas-lift bioreactors), using silicone membrane oxygenation to provide oxygen for large scale cell production (Fleischaker and Sinskey, 1981), adding an organic phase (often called oxygen vectors) to the system (Ede et al., 1995), adding a sample loop spiroid, wall baffles and center baffles to a continuous roller bottle reactor (Berson et al., 1998), introducing oxygen enriched air to the system, using hyperbaric air to aerate the bioreactor (Belo et al., 2003). The results from these modifications were promising, however, a simpler and more effective method to improve oxygen transfer was proposed in this study involving only adding a spiroid. This study demonstrated the ability of one novel rotating bioreactor with a spiroid to transfer oxygen to the liquid phase in the absence of living cells two times faster than did the same reactor without a spiroid. Were cells to be cultivated in this bioreactor, since the oxygen would be continuously consumed by the cells, the oxygen in the system would remain unsaturated; therefore,