Indian Journal of Biotechnology
Vol 14, July 2015, pp 394-401

The effect of agitation and aeration on production of cyclosporin A in batch cultures of *Tolypocladium inflatum* MTCC 557

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Received 24 January 2014; revised 19 October 2014; accepted 21 December 2014

The present study reports the effects of aeration and agitation on growth and production of the cyclosporin A (CyA) in batch fermentor cultures of *Tolypocladium inflatum* MTCC 557. Dissolved oxygen concentration, pH, dry cell wt, CyA titer and sugar utilization were continuously measured and determined. In the first step, the effect of agitation was evaluated by changing the agitation speed in the range of 250 to 450 rpm at 1 vvm. Further, after selecting the optimum agitation speed, the aeration rate was varied between 0.5 vvm to 1.0 vvm. Efficiency of aeration and agitation was evaluated through oxygen mass transfer coefficient (k_La). Maximum CyA production of 1274 mg/L with specific productivity of 0.152 mg/g.h was obtained at 350 rpm agitation and 0.75 vvm aeration. The k_La of the fermentation system supporting maximum production (350 rpm, 0.75 vvm) was 0.113 h^{-1}. The oxygen transfer rate (OTR), oxygen utilization rate (OUR), and specific oxygen uptake rates (qO_2) in the fermentation broth were also determined.

Keywords: Aeration, agitation, cyclosporin A, k_La, *Tolypocladium inflatum*

Introduction

Cyclosporin A (CyA) is a cyclic undecapeptide with a variety of biological activities including anti-inflammatory, immunosuppressive, antifungal and antiparasitic properties[1]. CyA is reported to be produced by submerged culture fermentation (SmF)[2], static fermentation[3], solid state fermentation[4], and also synthesized enzymically[5].

Various studies have been conducted on the effect of microbial strain, nutrient composition and environmental condition on the production of CyA in SmF[2,6-8]. However, there is scarcity of literature on effect of aeration and agitation on the CyA production. Both agitation and aeration are involved to different extent in overall mass and oxygen transfer in the process fluid. McNeil and Harvey[9] reported that agitation controls nutrient transfer and the distribution of air and oxygen, while aeration determines the oxygenation of the culture and also contributes to bulk mixing of the fermentation fluid, especially where mechanical agitation rates are low. Inadequate supply of oxygen is one of the major problems in industrial as well as lab-scale production of antibiotics, since oxygen is sparingly soluble in aqueous media. The conventional approach to this problem usually involves improvements in the design of the bioreactor, agitator and sparger, as well as the use of oxygen-enriched air. The fermentative productions of several important metabolites are influenced by the agitation and aeration[10-12]. In this context, the oxygen consumption in terms of oxygen utilization rate (OUR) by cells and oxygen transfer rate (OTR) into the system need to be understood. The OTR in a bioreactor depends on the liquid side mass transfer coefficient (k_L), the total specific surface area available for mass transfer (a), and the driving force in terms of concentrations[13-17].

The overall oxygen mass transfer coefficient (k_La) is often used as scale-up factor of fermentation systems. In fermentor scale-up, it is desirable to achieve the same k_La values at the larger scale as that was obtained in a laboratory scale during the development stage.

The OUR is one of the fundamental physiological characteristics of culture growth and has been used for optimizing the fermentation[13,18,19]. Usually the specific oxygen uptake rate (qO_2) is calculated from OUR, which is determined experimentally. OUR measurement has recently received due attention in different bioprocess studies[20-24].

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