ZENTRUM ANGEWANDTE CHEMIE

Institut für Technische Chemie

Partner in der Forschung

Institut für Technische Chemie, Callinstr. 5, 30167 Hannover

Leibniz Universität Hannover

Comparison of a novel continuously operated ceramic membrane bioreactor for the cultivation of shear stress-sensitive organisms to stirred tank reactor systems

C. Endres[1], R. Chen[1], S. Beutel[1], S.J. Fraser[2], W. Edwards[2] and T. Scheper[1]

1) Institut für Technische Chemie, Universität Hannover, Callinstr. 5, 30167 Hannover, Germany

2) Synexa Life Sciences, Cape Town, South Africa

Introduction

One of the major advantages of membrane-based reactor systems is the provision of an artificial environment for an increased biomass density and enhanced productivity. Synexa's Quorus bioreactors consist of ceramic capillary membranes contained within a disposable bioreactor housing. Due to its design it provides an optimal platform for the immobilization and cultivation of shear stress-sensitive microorganisms. Accordingly the reactor system is constructed to perform continuously operated cultivations for the production of valuable secondary metabolites or recombinant products.

Quorus LS

Mode of operation

- A biofilm is established in a submerged and oxygen-limited environment in the extracapillary space (ECS).
- With a sufficient thickness of the biofilm a radial nutrient gradient is established across the biofilm.
- Nutrient supply is achieved through a continuous feed into the ECS.
- Metabolic waste and secreted products are continuously removed by transportation through the capillary wall into the intracapillary space (ICS).

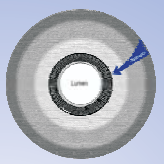

Fig. 1: Nutrient gradient during biofilm formation around the ceramic membranes in the Quorus LS bioprocess

Evaluation of productivity

- Cultivation of the facultative anaerobic lactic acid bacterium *L.lactis* PRA290 in a Quorus LS 0.22 L bioreactor and monitoring of the production of recombinant β-lactamase.
- Comparison to traditional fermentation vessels like shaking flasks, stationary flask cultures and a 3 L Biostat A plus.
- Quorus LS productivity per reactor capacity and total product output is significantly higher than in all other cultivation vessels.

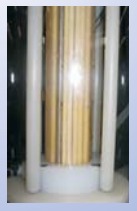

Fig. 2: Quorus LS 0.22 L reactor unit in operation

- Best suited for cultivations of facultative anaerobic or microaerophillic microorganisms
- Low shear stress environment
- Disposable and scalable ceramic membrane bioreactor
- Cell-free product stream
- Continuous removal of toxic metabolites and/or metabolic waste
- Exploitation of submerged biofilms for the production of secreted compounds, e.g. recombinant proteins
- Fully automated design and product sampling

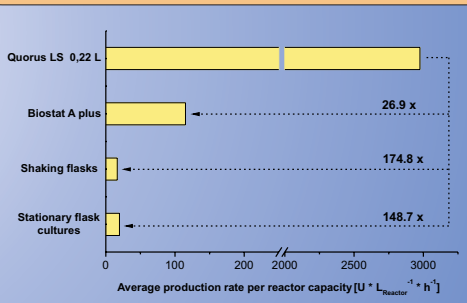

Fig. 3: Average production rate of a β-lactamase per reactor capacity in various cultivation vessels while cultivation of *L.lactis* PRA290.

Quorus GLS

Mode of operation

- Biomass is grown in the aerated ECS with nutrient medium flowing unidirectional from the lumen of the capillary membranes towards the ECS.
- With a sufficient thickness of the biofilm radial nutrient and oxygen gradients are established across the biofilm.
- The nutrient gradient is maintained in such a way, that it is high enough to support primary growth of the microorganism and low enough to induce secondary metabolite production.
- Secreted products are collected with medium stream passing the biofilm.

Fig.4: Quorus GLS intra-capillary space (ICS) for nutrient supply.

Evaluation of productivity

- Cultivation of the fungus *A.niger* in a 50 membrane Quorus 2 L bioreactor and monitoring of the production of a secreted recombinant protein.
- Comparison to traditional fermentation vessels like shaking flasks, 3 L Biostat A plus and 15 L Biostat C.
- Stable protein production in the Quorus GLS bioreactor for more than 40 days.
- Quorus GLS space-time-yield is significantly higher than in all other cultivation vessels.

Fig.5: Aerated extracapillary space (ECS) for biofilm formation and product recovery.

- Best suited for steady-state cultivations of aerobic filamentous microorganisms
- Stable and continuous process
- Fully automated design
- Disposable and scalable ceramic membrane bioreactor
- Low shear stress environment
- Steady-state biofilm for the production of secreted compounds such as recombinant proteins or secondary metabolites

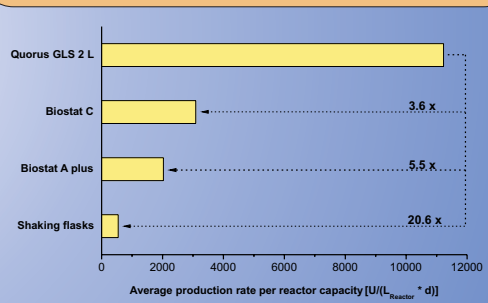

Fig. 6: Average production rate of a recombinant protein per reactor capacity in various cultivation vessels while cultivation of *A.niger*.

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