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Microbial cultivation in different scales in the CELL-tainer® rocking single-use bioreactor

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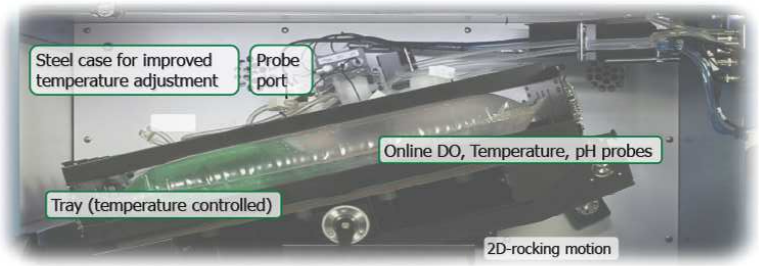
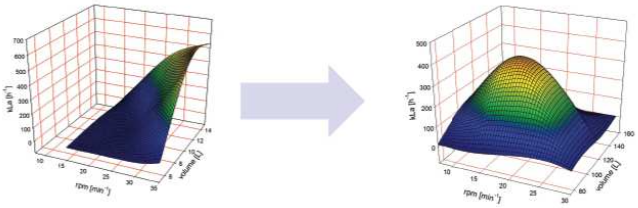
Background

Single-use bioreactors are applied in the biopharmaceutical industry for mammalian cell culture processes. The low gas-liquid mass transfer coefficient generally achieved in these systems does not allow for the compatable application of microbial processes in these bioreactor systems. The CELL-tainer® technology combines a vertical and horizontal movement in a rocking bioreactor concept, so that the turbulence and power input is intensified. In this system, mass transfer rates comparable to stirred tank reactors are achievable. Thus, volumetric oxygen transfer rates (k_La) of over 400 h^{-1} could be achieved. The scale-up of *Escherichia coli* nutrient-limited fed-batch cultivations from 15L to 150L cultivation scale in the CELL-tainer single-use bioreactor has been conducted sucessfully. A final biomass concentration of 45 gL^{-1} within 24 hrs was obtained proving the suitability of this reactor for the application of bacterial processes. The combination of intelligent software sensor control and improving sensors lead to improved control of bacterial fed-batch processes. The availability of single-use bioreactors for microbial cultivations widens their potential, not only in biopharmaceutical processing, but also as a pre-culture bioreactor for large processes and as a tool in bioprocess development.



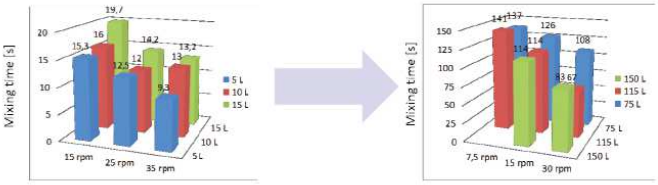
The CELL-tainer 20L and 200L concept as used in this study. Both systems allow the adjustment of the rocking angle, flow rates and filter diameters to the needs of microbial application.

The oxygen-liquid mass transfer



k_La values obtained in water at primarily deoxygenated water at different filling volumes and rocking rates in the CELL-tainer 20L (left) and CELL-tainer 200L (right). In the larger system, a distinct region where eddy formation occurs is characterized by high k_La values.

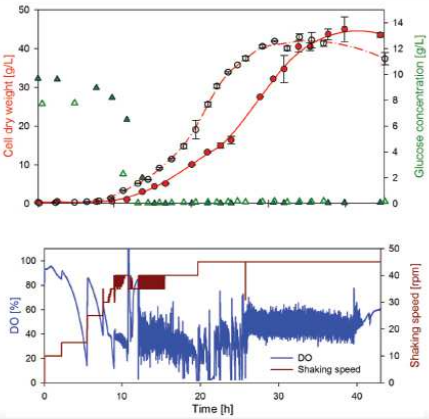
The mixing time



The mixing times at the CELL-tainer 200 L (right) were higher than in the smaller CELL-tainer 20 L system (left). However, the mixing time did not exceed 2 minutes under suitable cultivation conditions, which is still acceptable for microbial application.

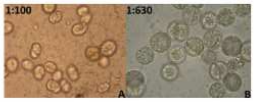
Escherichia coli fed-batch cultivation

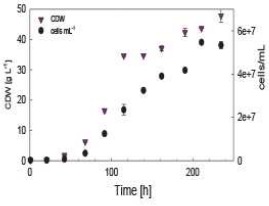
Cultivation experiments had been performed in a scale of 12 L (unfilled symbols) and 120 L (filled symbols) at 30°C and pH 7.0. Following a growth phase, a maltogenic amylase was produced after induction (24 h). In the larger scale, reduced flow meter capacity led to slightly lower feed and growth rates in order to avoid oxygen limitation.
In the lower graph, the distribution of the dissolved oxygen concentration and the rocking speed throughout the timecourse of the cultivation in the 12 L scale is depicted.



Marine microalgae cultivation

The marine mixotrophic algae *Cryptecodinium cohnii* produces polyunsaturated fatty acids. Since cells are shear-sensitive and marine media causes corrosion of common stainless steel, the application of single-use bioreactors worth high k_La values is an interesting alternative. Depicted is the proper shape and growth in a fed-batch cultivation in the 12 L scale in the CELL-tainer bioreactor.





Conclusions

The CELL-tainer at both scales is applicable for microbial fermentation providing comparable results to traditional stainless steel reactors at various scales.
This enables new fields of application for single-use systems, while their typical advantages in application, such as quicker turnaround time, contamination risk reduction, operational flexibility, reduced validation requirements and significant cost savings are maintained.

Acknowledgements
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Literature: N.M.G. Oosterhuis, P. Neubauer and S. Junne: Single-Use Bioreactors for microbiol applications, Pharmaceutical Bioprocessing, June 2013, Vol. 1, No. 2, Pages 167-177 , DOI 10.4155/pbp.13.19
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