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Challenges and status: Single-use Bioreactors for Microbial Processes

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Nowadays single-use bioreactors are fully accepted in the biopharmaceutical industry. Reactors up to 2000L working volume are commonly used. However, these bioreactors are limited in terms of mass-transfer and mixing capabilities and therefore only suited for application in mammalian cell culture. Single-use processing offers many benefits like cost reduction, flexibility, reduction of contamination risks, etc. These benefits apply for both microbial processes as for mammalian processes.

Additionally, for the use of marine microorganisms the application of single-use bioreactors (SUB) offers a possibility to circumvent problem of corrosion which occurs in steel bioreactors due to the high chloride ion concentration in the media when the early stage of process development or the need for multi-purpose devices does not allow the investment in process-specific infrastructure. However, marine production processes can demand for high gas mass transfer rates, e.g. in the case of *Crypthecodinium cohnii*, a heterotrophic algae applied for the production of the polyunsatured fatty acid docosahexaenoic acid. *C. cohnii* cells are highly sensitive to shear-forces. In general, unfavorable cultivation conditions lead to a high batch-to-batch variation, and thus to a random process development and optimization.

In this paper we describe experience of the use of different single use bioreactors for the high cell density cultivation of *C. cohnii* and other microorganisms. Specific parameters we looked at were the gas transfer efficiency as an important parameter for high cell and product yields as well as the opportunity for expansion of the culture over a wide volume range.

Among various SUBs, which were tested, only the 2-D wave-mixed CELL-tainer® showed a high oxygen mass transfer at comparably low shear forces, and hence provided a very vital culture.[1, 2] In order to broaden the range of the working volume, expansion channel blocks were applied, which allow performing cultivations from 150 ml to 20 L without reinocculation.

However, the scalability of a wave-mixed system is challenging due to the restricted knowledge of classical engineering parameters. Therefore, the physiologic and morphologic constitution of the cells was considered to prove the suitability of the SUBs at scales from the mL to the 120 L range. Therefore a novel on-line photo-optical instrument (SOPAT) for the analysis of cell shapes, and lipid droplet accumulation was applied. It allowed a direct insight into the stage of growth, population homogeneity, and fatty acid production. Although it is hardly feasible to maintain identical cultivation conditions from the µL to the m³ scale, the combination of engineering parameters and process analytical tools led to the overall achievement of suitable cultivation conditions. The presented on-line method in relation to the developmental strategy over different scales is relevant for the development of plant and other cell culture processes, while contributing to reduced development times and costs.

[1] Hillig F, Porscha N, Junne S, Neubauer P. Growth and docosahexaenoic acid production performance of the heterotrophic marine microalgae Crypthecodinium cohnii in the wave-mixed single-use reactor CELL-tainer. Eng Life Sci. 2014 May;14(3):254-63.

[2] Junne S, Solymosi T, Oosterhuis N, Neubauer P. Cultivation of Cells and Microorganisms in Wave-Mixed Disposable Bag Bioreactors at Different Scales. Chem-Ing-Tech. 2013 Feb;85(1-2):57-66.