GE Healthcare
Life Sciences

Growth of high-cell density microbial cultures in a single-use fermentor system

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Abstract

Here we show the performance of a single-use Xcellerex™ XDR-50 MO fermentor system when used in high-cell density cultivations of *E. coli* producing a domain antibody (Dab) and of modified *Pseudomonas fluorecsens (P. fluorescens)* producing a monoclonal antibody (MAb) (Fig 1). Both the achieved microbe densities and product yield were shown to be consistent with the performance of conventional stainless steel and glass bioreactor systems.

Fig 1. XDR-50 MO fermentor system.

Introduction

Microbial processes are widely used for industrial production of biopharmaceuticals. Due to the historical limitations of single-use technologies, biomanufacturers have traditionally been referred to the use of stainless steel equipment for these processes. Bioreactors designed for mammalian processes fall short of meeting the unique requirements of production in microbial processes in terms of, for example, oxygen transfer capacity and temperature control. Xcellerex XDR-50 MO fermentor system is purpose-designed and built to overcome the mammalian single-use system limitations in fulfilling the needs of a microbial process. The culture vessel features a dimpled jacket heat transfer surface for efficient cooling and heating of the culture. Robust agitation is provided by a powerful magnetic drive and a two-stage impeller, resulting in a high oxygen transfer to the culture medium.

XDR-50 MO design features

As shown in Figures 2 and 3, baffle geometry and agitation rate have significant impact on oxygen transfer rate (OTR). As indicated in Figure 4, working volume has inverse impact on OTR. Oxygen content has highest impact on OTR (Fig 5), whereas when flow rate is above 1 VVM*, OTR is saturated with no beneficial effect as from increasing flow rate (Fig 6). The cooling capacity for XDR-50 MO is shown in Table 1.

* Gas volume flow per unit of liquid volume per minute (volume per volume per minute)

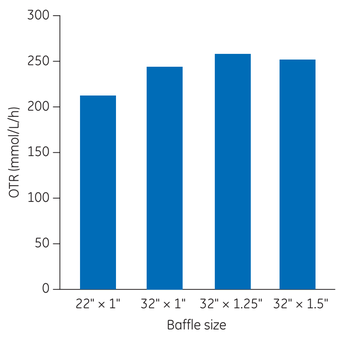

Fig 2. OTR versus baffle size (25 L, 350 rpm, 1 VVM, 100% air).

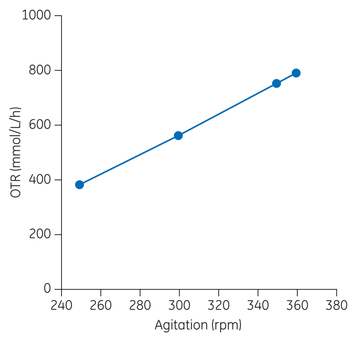

Fig 3. OTR versus agitation (35 L, 1 VVM, 50% air, 50% O_2, 32" × 1.25" baffles).

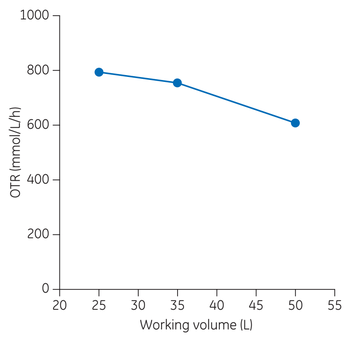

Fig 4. OTR versus reactor volume (350 rpm, 1 vvm, 50% air, 50% O_2, 32" × 1.25" baffles).

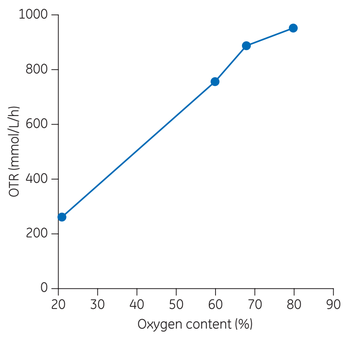

Fig 5. OTR versus %O_2 in sparge gas (35 L, 350 rpm, 1 VVM, 32" × 1.25" baffles).

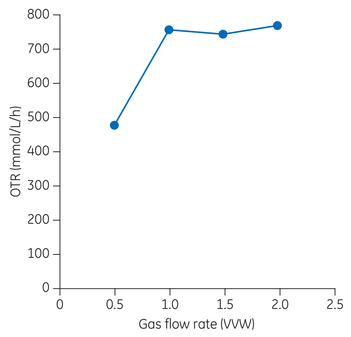

Fig 6. OTR versus sparge gas flow rate (VVM) (35 L, 350 rpm, 50% air, 50% O_2, 32" × 1.25" baffles).

Table 1. Cooling capacity

Mass of water	50 kg
Agitation	350 rpm
Aeration	none
Temp. start	37°C
Temp. end	32°C
Heat removal rate	5587 BTU/h (1637 W)

Cell growth and production in *E. coli* fed-batch cultures

A domain antibody (Dab) was produced in parallel fed-batch cultures of *E. coli* using XDR-50 fermentor and a reference stainless steel system from Belach Bioteknik AB. Microbial growth achieved in XDR-50 MO fermentor was comparable with that of the reference bioreactor (Fig 7). Product titers were also similar between the systems: 2 g/L for XDR-50 MO and 2.2 g/L for the reference bioreactor.

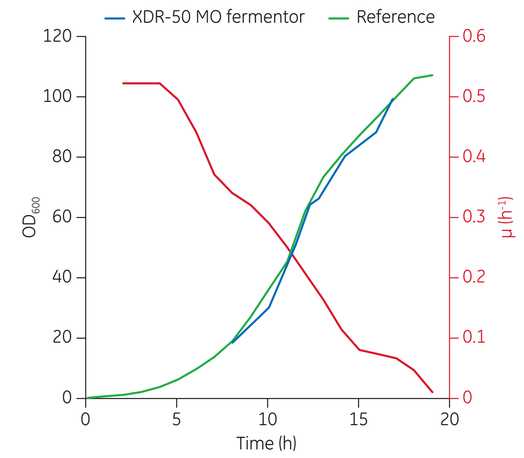

Fig 7. Cell growth in a 30 L XDR-50 MO fermentor culture versus in a 10 L culture in the reference stainless steel bioreactor.

Cell growth and production in *P. fluorescens* fed-batch cultures

A monoclonal antibody (MAb) was produced in parallel fed-batch cultures of *P. fluorescens* using XDR-50 fermentor and a reference glass bioreactor from New Brunswick Scientific. The final OD_{575} of the cultures ranged from 193 to 375 and the MAb yields from 46 to 72 mg/L. Both the achieved culture densities and MAb yields are consistent between the systems (data not shown). Figure 8 displays two parallel runs in the XDR-50 fermentor, exhibiting high cell growth.

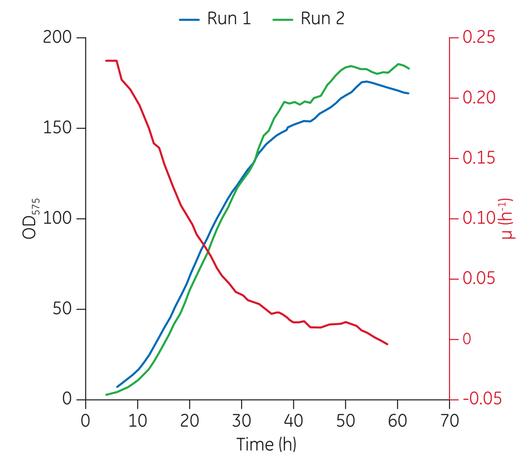

Fig 8. Cell growth in two parallel 30 L XDR-50 MO fermentor cultures.

Discussion

The fermentor is designed to meet the unique requirements of microbial cultures in terms of, for example, high oxygen transfer capacity and high cooling capacity. As shown in applications with *E. coli* and *P. fluorescens*, the XDR-50 MO fermentor is capable of delivering both cell growth and protein production equivalent to those of conventional stainless steel and glass microbial fermentor systems. The improved features and benefits of this single-use system eliminates the need for time-consuming cleaning-in-place and sterilization-in-place operations and offers increased operational flexibility for the biomanufacturer using microbial processes.

Conclusions

- The single-use Xcellerex XDR-50 MO supports cell growth comparable with conventional fermentor systems
- A system design with a powerful drive enables high oxygen transfer rates > 500 mmole L^{-1} h^{-1}
- The XDR-50 MO cooling capacity is sufficient to support high-density microbial cultures

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