Characterization of Xcellerex XDR single-use bioreactor systems

Intellectual Property Notice: The Biopharma business of GE Healthcare was acquired by Danaher on 31 March 2020 and now operates under the Cytiva™ brand. Certain collateral materials (such as application notes, scientific posters, and white papers) were created prior to the Danaher acquisition and contain various GE owned trademarks and font designs. In order to maintain the familiarity of those materials for long-serving customers and to preserve the integrity of those scientific documents, those GE owned trademarks and font designs remain in place, it being specifically acknowledged by Danaher and the Cytiva business that GE owns such GE trademarks and font designs.

cytiva.com

CY15142-12Jul20-PT

GE Healthcare

Characterization of Xcellerex™ XDR single-use bioreactor systems

Andersson, A., Castan, A., Sjöberg Gällnö, K., Smith, T., Francis, E., Burdick, J-A., Lisle, L.

GE Healthcare Bio-Sciences AB, SE-75184 Uppsala, Sweden

Introduction

Single-use bioreactor systems are widely used in biomanufacturing due to the many advantages that come with disposables, including reduced cross-contamination risk and shorter batch changeover time. The main challenge, however, when transferring biomanufacturing processes from stainless steel to single-use vessels is insufficient knowledge about the physical performance of the equipment. Data on oxygen transfer capacity, power input, and mixing time is essential for effective process transfer. In this study, Xcellerex XDR bioreactor systems were characterized with respect to volumetric oxygen transfer rate, mixing time, heat transfer, and power input to define ranges for efficient process control and to establish a scalable design space. The resulting data provide the information required for process transfer to the XDR systems (Fig 1), and will also facilitate transfer between larger and smaller process scales.

Fig 1. The complete range of XDR bioreactor systems, available with maximum working volumes ranging from 10 to 2000 L.

Material and methods

K_La was determined with the gassing out method using design of experiments (DoE), with volume, agitation, and air flow rate as variables. For XDR-10 up to XDR-200, all sparger types were tested (2 µm, 20 µm, 0.5 mm, 1 mm). The 2 µm and 20 µm spargers were tested for the XDR-1000 and XDR-2000 systems, respectively.

Mixing time was measured at multiple locations in the bioreactors (Fig 2). Mixing times was determined by measuring time to reach 95% of the pH step change (t_{m95}). Acid was added from the top of the bioreactor. To establish starting conditions, base was added. Agitation and volume were used as variables in the DoE setup. To display the worst-case scenario, probe location with the longest mixing time in each run was used to generate the models.

The obtained k_La coefficients and mixing times were modelled in the DoE software, MODDE™ version 11.0.0.1717 (Umetrics AB), to assess k_La and mixing time for any volume, agitation, and air flow setting within the tested ranges. Experimental settings are summarized in Table 1.

Power input was assessed by measuring the motor current at variable agitation rates under gassed and ungassed conditions. The motor current was recorded and converted into torque using motor-specific torque constants (Kollmorgen, Radford, VA, USA). To compensate for the power loss due to friction in the motor and impeller, power was measured during zero load conditions for each tested agitation setting. Along with the power input determination, a scalability assessment in terms of oxygen transfer rate was performed.

Heating/cooling was tested for three different working volumes and three temperature intervals (20°C–37°C, 37°C–5°C, and 5°C–20°C) at constant agitation. Time required to heat/cool the liquid was established by measuring the time to reach 95% of the temperature step change (t_{95}). Triplicate experiments were performed at the mid-point volumes for all temperature intervals tested to assess reproducibility.

Test liquid used for power input and k_La experiments consisted of 6 g/L NaCl, 1 g/L poloxamer 188, and 50 ppm Antifoam C in purified water. Mixing time experiments were performed in 1 mM PBS using 0.5 M HCl/NaOH in 1 mM PBS to shift pH. For heating/cooling experiments, 6 g/L NaCl in purified water was used.

Table 1. Experimental settings for k_La and mixing time experiments

Parameters	XDR-10	XDR-50	XDR-200	XDR-1000	XDR-2000
Liquid volume (L)	10.0 7.25 4.5	50 32.5 15*	200 120 40	1000 600 200	2000 1200 400
Agitation (rpm)	40–360	40–360	30–350	15–140	25–115
Air flow rate (L/min)	0.05–1	0.25–5	0.5–5	1–10	2–20
Max. no. of pH probes used	4	6	8	9	9
Temperature	37°C				
Impeller direction	Up-flow				

* Heating/cooling times were tested using 22 L as minimum working volume

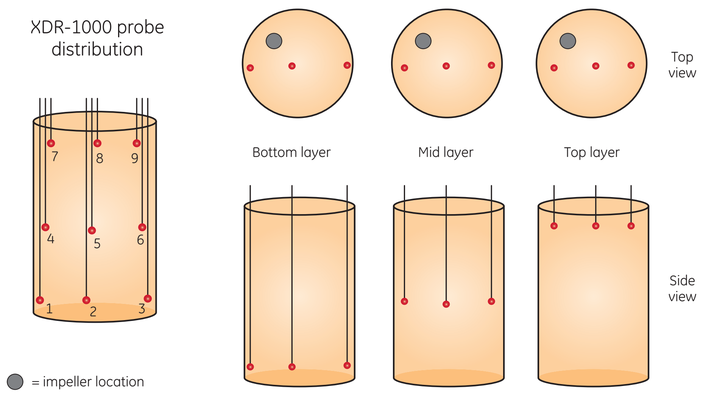

Fig 2. pH probe distribution for mixing time experiments in XDR-1000.

Results

In Figure 3, modeled k_La values at fixed P/V and VVM using the 20 µm sparger are shown.

Figure 4 displays an excerpt of the results from determining mixing time (t_{m95}) for the XDR-1000 system at variable agitation and volume.

An extract from heating/cooling experiments (heating from 20°C to 37°C) is shown in Figure 5.

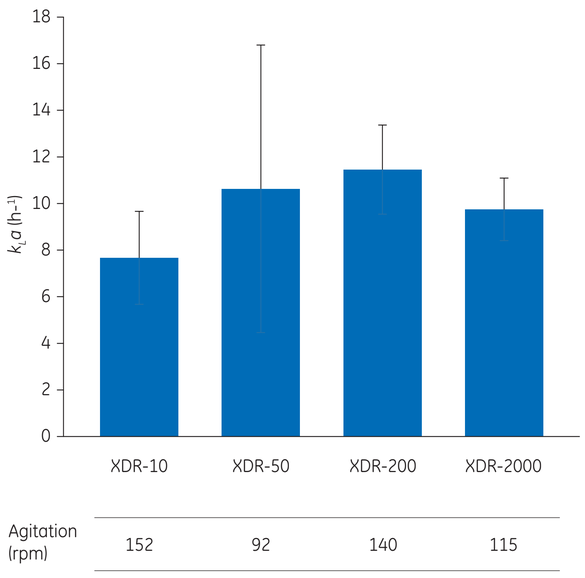

Fig 3. k_La for XDR bioreactors at max. working volume using 20 µm micro-sparger at a constant P/V of 30 W/m³ and air flow rate of 0.01 VVM. Error bars correspond to upper and lower limits of a 95% confidence interval.

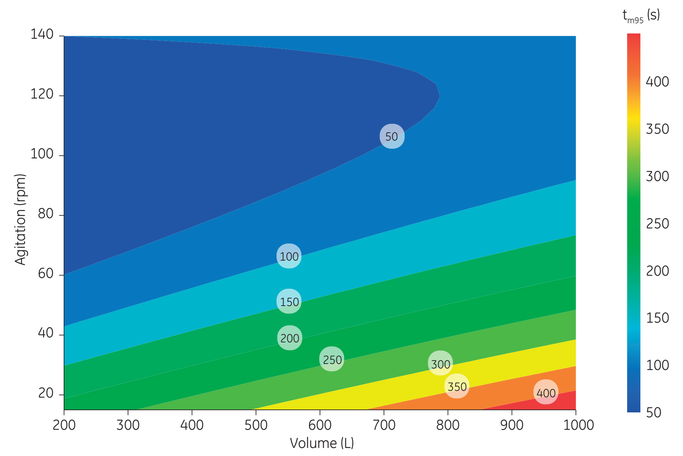

Fig 4. Response contour plot showing mixing time (t_{m95}) for XDR-1000 at variable volume and agitation. The model fit (R^2) is 0.96, the model predictability (Q^2) is 0.92, and the residual standard deviation (RSD) of the model is 30 s.

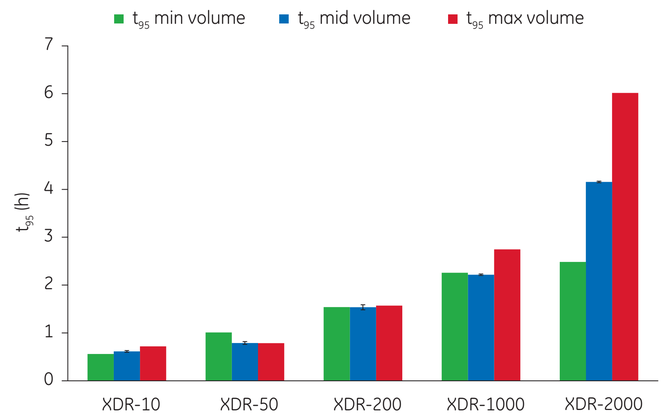

Fig 5. Time required to heat the liquid contents from 20°C to 37°C for all tested bioreactor sizes at minimum, mid-point, and maximum volume. Error bars correspond to one standard deviation.

Conclusions

- XDR single-use bioreactor systems were successfully characterized for oxygen transfer rate, mixing time, power input, and heating/cooling time.
- Measured k_La values ranged from 0.2 to 107 h^{-1}. At a P/V of 30 W/m³ and a gas flow of 0.01 VVM, using the 20 µm sparger, k_La values between 8 h^{-1} and 12 h^{-1} were predicted for the tested bioreactors. Assuming a cell-specific oxygen consumption rate of 0.2 pmol/cell/h, using the P/V, gas flow, and sparger configuration outlined above, cell densities between 10 and 35 million viable cells/mL can be supported throughout the tested bioreactor range depending on the oxygen supplementation level (0% to 50% of mass flow).
- Mixing times for all bioreactors were in the same range as for the XDR-1000 at similar power input, but with slightly shorter mixing times for the smallest scale. The difference between probe positions was moderate, with averages of 5 s for XDR-10 and 68 s for XDR-1000 between the probe positions resulting in the longest and shortest t_{m95} for each run, indicating effective mixing across the whole bioreactor range.
- The measured heating and cooling times generally increased with bioreactor size, and the time required for cooling was found to be longer than for heating. The heating/cooling rates (max. dT/t) determined can be used to predict the time for any specific temperature increase/decrease within the temperature ranges tested.

29242415 AA 11/2016