Characterization of Xcellerex XDR single-use bioreactor systems

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CY16566-15Sep20-PT

Characterization of Xcellerex™ XDR single-use bioreactor systems

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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 (Fig 1). 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, and 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.

Materials and methods

The volumetric mass transfer coefficient (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 were 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, the 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 modeled 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 active ingredient of Antifoam C in purified water. Mixing time experiments were performed in 1 mM PBS using 500 mM 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

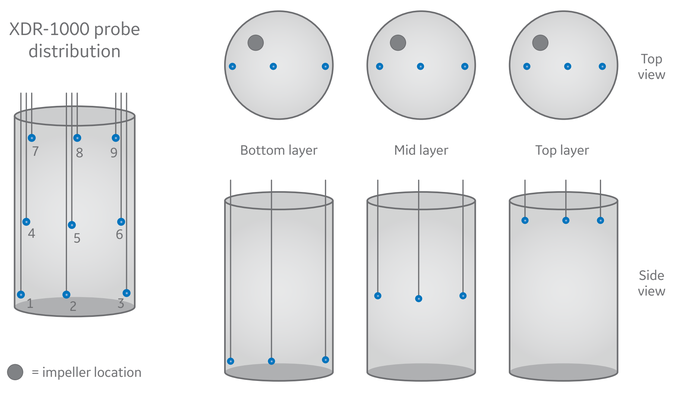

Fig 2. pH probe distribution for mixing time experiments in XDR-1000.

Results

In Figure 3, modeled k_La values at fixed power/unit volume (P/V) and vessel volumes/minute (VVM) using the 20 µm sparger are shown.

Figure 4 displays an excerpt of the mixing time study. The contour plot shows mixing time (t_{m95}) for the XDR-1000 system at variable agitation and volume.

An extract from heating/cooling experiments is shown in Figure 5.

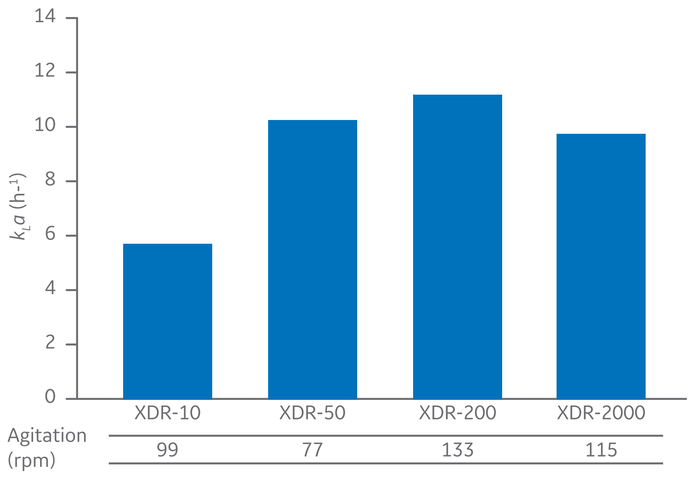

Fig 3. k_La for XDR bioreactors at max. working volume using 20 µm microsparger at a constant P/V of 33 W/m^3 and air flow rate of 0.01 VVM.

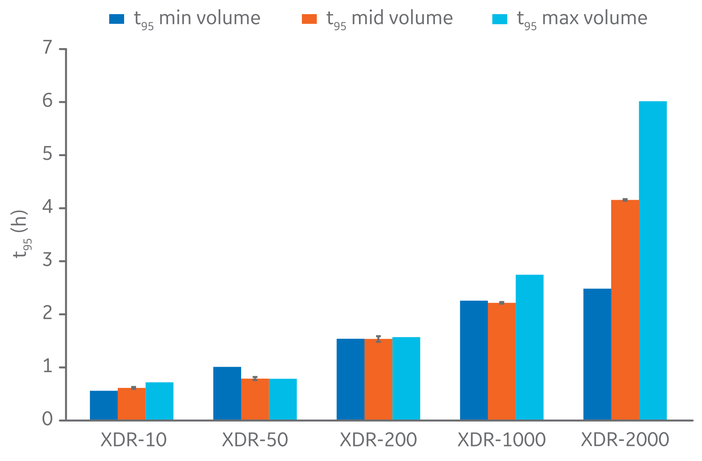

Fig 5. Time required to heat the liquid contents from 20°C to 37°C for all tested bioreactor sizes at minimum, mid-point, and maximum volume. Error bars correspond to one standard deviation.

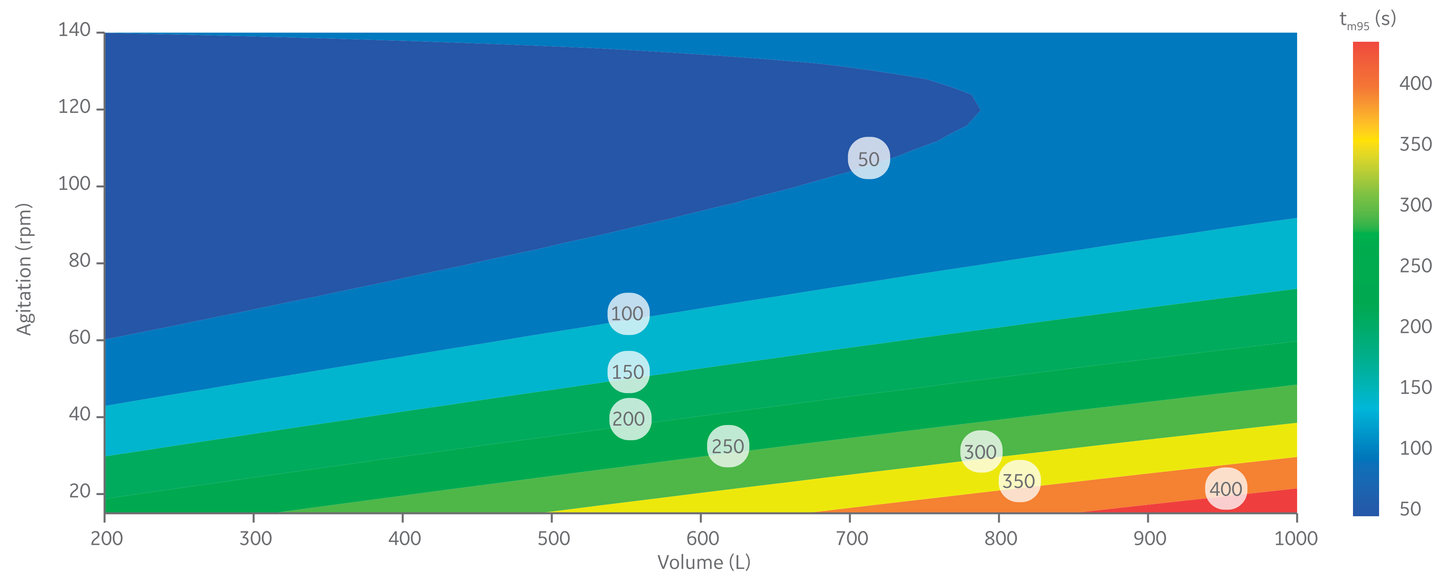

Fig 4. Response contour plot showing mixing time (t_{m95}) for XDR-1000 at variable volume and agitation. The model fit (R^2) is 0.96, the model predictability (Q^2) is 0.92, and the residual standard deviation (RSD) of the model is 30 s.

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 in the XDR bioreactors ranged from 0.2 to 107 h^{-1} depending on agiation and air flow rate. At a P/V of 33 W/m^3 and a gas flow of 0.01 VVM, using the 20 µm sparger, k_La values between 6 h^{-1} and 11 h^{-1} were predicted by the DoE model for tested range of XDRs. To give an example: At 50% oxygen to air mass flow, a k_La of 10 h^{-1} will support a cell culture of up to 20 million viable cells/mL at a DO of 40%, assuming a cell-specific oxygen consumption rate of 0.3 pmol/cell/h.
- The mixing time difference between the probe positions was moderate. On average there was a 5 s difference between the probe positions resulting in the longest and shortest t_{m95} in the XDR-10 and a 68 s difference in the XDR-1000, 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.

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KA458200917PO