ADDRESSING THE GASSING RATE IN BIOREACTOR UPSCALING – IS VVM A RELIABLE PARAMETER?

Common approaches for the scale-up of bioreactors use the gas flow coefficient (vvm) as a criterion for volumetric flow rates. Besides being the most common decisive parameter when it comes to the scaling of the gassing rate, a defined vvm is frequently used in the context of process validation, and therefore considered essential for qualification. ZETA called the reliability of this parameter into question and evaluated the scaling competence of vvm in a study performed in the context of commissioning an upstream production plant. Based on the results of the study, ZETA strongly recommends not relying solely on this parameter, as it would certainly produce erroneous results in scaling. A comprehensive view of the highly complex system is essential for optimal scaling.

Introduction

One of the primary difficulties when establishing a biopharmaceutical production is ensuring the proper transfer of the process. This becomes especially crucial when working with living microorganisms, as obtaining critical process parameters is essential for productive and profitable production. Therefore, careful attention must be paid to the bioreactor, which creates the microorganisms' environment. To assist customers with the process transfer and optimize potential processes, ZETA examines the performance of the bioreactors they provide and makes detailed information available. The ZETA white paper The Critical Role of Predictive Bioreactor Characterization in Pharmaceutical Process-Based Upscaling[1] summarizes this characterization approach.

Reliable and sound data is required for the examination of existing strategies and for the development of new scale-up strategies. A highly valuable source of data are characterizations of bioreactor systems conducted using proven methodologies. The white paper mentioned above describes a process-based approach, in which the scale-up of bioreactor systems is based on the specific process conditions. These are characterized by performance parameters, such as heat transfer rate, mixing time, power input, or oxygen transfer rate. Reliable measuring methods with comparable results are essential for process-based scaling of bioreactor systems, because it must be ensured that the process parameters remain within a defined design space, and that the optimal conditions are fulfilled. ZETA has developed strategies for the assessment of several important performance parameters and performs bioreactor characterizations based on these measurements and calculations. Accordingly, ZETA can refer back to a large amount of valuable data and know-how resulting from their ample experience in bioreactor design, characterization and optimization. New scaling strategies can then be developed based on standard scaling procedures, and a growing database of measured process parameters. The scale-up approach proposed by ZETA involves a deep understanding of the process itself and a clear definition of critical process parameters. These

[1] Access via https://www.zeta.com/de/newsroom/blog/detail/white-paper-charakterisierung-von-bioreaktoren-im-prozessbasierten-upscaling.html

parameters can then be challenged and specified for the bioreactor design, and, most importantly, verified via characterization during FAT and SAT. This approach guarantees the highest product quality and maximum yield as well as compliance with the FDA guidelines for process validation.

Scaling of the gassing rate

This article, which focuses on the challenges of scaling the gassing rate across different bioreactor scales, presents recent findings as a follow-up to the afore-mentioned white paper.

Ensuring an efficient supply of oxygen is crucial for cell growth and can be considered one of the central challenges in bioreactor design and scaling. Reliable design of the gassing system is particularly essential when it comes to transferring the process from laboratory to production scale. A core parameter widely used in the industry to scale the gassing rate is vvm – "vessel volumes per minute" – the gas volume flow [L/min] from the sparging system per working volume of the bioreactor [L].

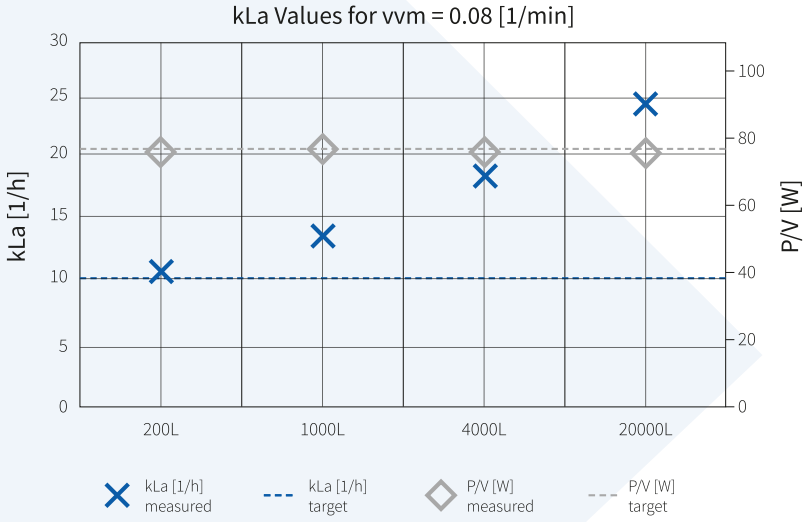


Figure 1: Measured kLa values at a set vvm (0.08 min-1) at different vessel sizes

Standard scaling approaches are based on geometric similarity and proceed by calculating volumetric power input P/V [kW/m^3] and the volumetric gassing rate vvm [1/min], and keeping these values constant. The kLa value and, therefore, the oxygen transfer rate (OTR) are then simply deduced from these specifications. However, since the size distribution and residence time of the gas bubbles are the key driving factors for the OTR, it is questionable whether they are sufficiently reflected within such a scaling approach. ZETA put this to the test via a study in a bioreactor train – with remarkable results.

On trial: vvm as a scaling parameter

Experiments were performed in a bioreactor line with vessel volumes of 200 L, 1000 L, 4,000 L, and 20,000 L, respectively. The vvm and specific power input were kept constant in each vessel and kLa values were determined by the dynamic step method, as recommended by DECHEMA (a German-based expert network for chemical engineering and biotechnology). The study showed that with increasing bioreactor volume, the kLa value increases dramatically, regardless of the constant vvm and specific power input (see Figure 1).

What could be the explanation for this behavior? The reason is that vessel volume and diameter do not scale to the same power (see Table 1). This leads to the fact that, at the same H/D ratio, the residence time (t_s) of the gas bubbles increases with the volume of the vessel. The same applies to the superficial velocity (v_s). Assuming a similar bubble size distribution, the result is a much higher surface area of gas bubbles. All of this has a direct impact on the kLa value.

Acceptance tests and performance optimization

The study was conducted during the commissioning of an upstream production plant. A specific vvm had been defined and was achieved as acceptance criterion. In addition to validation, ZETA provided the required process parameters to operate the 20k bioreactor with a performance consistent with the 200 L scale.

Conclusion

Using vvm as a scaling parameter for the oxygen transfer rate results in significantly higher kLa values for large bioreactor volumes. This issue can be addressed by reducing gassing rates during

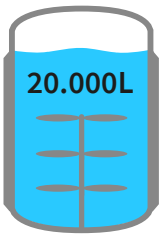
		200L	20.000L
			
		H/D=1.6	
		vvm=0.08	
Inner diameter D_i	[mm]	500	2550
Height H	[mm]	877	4080
Volumetric flow rate $\dot{V}$	[L/min]	16	1600
Superficial velocity v_s	[m/s]	1.1 E-3	5.2 E-3
Residence time t_s	[s]	3	12

Table 1: Comparison of 200 L and 20,000 L bioreactors. Residence time (t_s) and superficial velocity (v_s) vary significantly at the same H/D value and volumetric gassing rate.

production. However, this scaling approach leads to a large variation in the design spaces, and to oversizing of the gassing and venting systems. By comprehending the correlation between the gas flow rate and the OTR, the process can not only be appropriately scaled, but can also be optimized in terms of control strategy and energy efficiency. ZETA's future studies will demonstrate that it is possible to achieve a much more sustainable operation while maintaining the same process performance.

In general, reliable bioreactor design calls for a process-based scaling approach, focusing on the performance of a system that ensures an optimal environment for cell cultivation. How does this work in practice? What role does predictive bioreactor characterization play in pharmaceutical process-based upscaling? These questions are addressed in ZETA's white paper The Critical Role of Predictive Bioreactor Characterization in Pharmaceutical Process-Based Upscaling [1].

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ABOUT ZETA

The ZETA Group, with 1.200 highly qualified employees and 27 subsidiaries worldwide, specializes in the design, manufacturing, automation, digitalization and qualification of customized biopharmaceutical facilities for aseptic process solutions. ZETA acts as a one-stop shop, combining plant engineering with HVAC, cleanroom and BMS/EMS design.

Biopharmaceutical active ingredients, such as anti-cancer drugs, insulin, vaccines and infusions are produced in these highly complex, "tailor-made" facilities. ZETA supports its customers along the entire drug development and manufacturing pathway with sophisticated solutions from laboratory to industrial production scale. Through its Smart Engineering Services, ZETA creates digital twins of process plants and has thus established itself as a market leader for digital solutions in the pharmaceutical and biotech industry.