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# Small-scale bioreactors: challenges in experimental determination of hydrodynamic stress in stirred vessels

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The rapid development of human mesenchymal stem cell (MSCs)-based cell therapies creates a strong demand for scalable, controlled, and reproducible manufacturing processes capable of delivering clinically relevant cell numbers. Bioreactor systems fulfill these requirements, however there is the need for efficient bioprocess design and optimization. During such cultivation, MSCs are exposed to complex hydrodynamic forces generated by mixing and aeration. Although adequate mixing is essential for efficient heat and mass transfer, maximum hydrodynamic stress ($\tau_{max}$) can affect cell viability and productivity. Direct evaluation of these effects using cell-based culture experiments is both time-consuming and inefficient, highlighting the need for alternative approaches to characterise $\tau_{max}$ in bioreactor systems.

In this study, shear-stress-sensitive aggregates, based on polymethylmethacrylate nanoparticles, were used as low-cost universal probes for $\tau_{max}$ characterisation in stirred bioreactors. Conventionally, aggregate size is determined by static light scattering (SLS); however, this approach requires relatively large sampling volumes, which limits its applicability in small-scale bioreactor systems and results in discontinuous and time-intensive analysis. To address these limitations, we developed and implemented a low-volume analytical approach based on optical microscopy image analysis for aggregate size determination. An optical flow-through cell was designed to allow continuous sampling and was tested using the high-throughput ambr®250 mL bioreactor system equipped with multiple impeller configurations. The comparative analysis demonstrated strong agreement between microscopy-based measurements and conventional SLS results, indicating that the proposed method can fully substitute SLS for $\tau_{max}$ characterisation. In addition, the approach enables continuous monitoring of particle size while reducing the sampling volume by approximately one order of magnitude.

The presented method provides an effective tool for real-time in situ characterisation of $\tau_{max}$ in bioreactor systems. Improved quantification of hydrodynamic forces in stirred and aerated bioreactors will support more reliable scale-up and scale-down strategies and contribute to enhanced reproducibility and standardisation of MSCs cultivation processes.