STUDY ON MIXING AND FLUID DYNAMICS IN SINGLE-USE SHAKEN SYSTEMS

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Bioreactors are widely used in a range of applications, including the food/drink, pharmaceutical and medical industries. Stirred Tank Reactors (STRs) are the most widely used and rely on mechanical stirrers to achieve the optimal fluid motion, and their flow dynamics has been extensively studied for a broad combination of operating conditions (Ducci and Yianneskis 2005, 2007, Escudie and Line 2003). Orbitally Shaken Reactors (OSRs) promote agitation through the orbital motion of the bioreactor, which induces sloshing of the free surface. Their flow dynamics has been mainly assessed for lab scale reactors of cylindrical cross-section, while few studies in terms of mixing and fluid dynamics are available for unconventional shapes at limited scales. During early stages of bioprocess development, single-use ml-scale shaken multi-well plates are commonly used for scale-down studies as they allow a large number of experiments to be performed using small amounts of material. However, very few studies published on shaken bioreactors have thoroughly studied the engineering aspects and the hydrodynamics at such a small scale, thus resulting in a lack of accurate scaling correlations between shaken and large scale conventional bioreactors. The flow in orbitally shaken reactors has been characterised by Weheliye *et al* (2013) and Ducci and Weheliye (2014) and a scaling law has been developed for two cylindrical reactors with internal diameters of 10 and 13 cm. However, the understanding of reactors with square shape is still very limited despite they have a number of practical applications. For example, two different disposable shaken reactors with square cross-sections have been used by Stettler et al (2007) for transient gene expression. The aim of this work was twofold – (i) to estimate the mixing time in microwell plates of different geometry and determine an effective scaling parameter between micro-scale and lab-scale reactors and (ii) to determine the fluid dynamics in square reactors and identify analogies with baffled stirred tanks.

In the first part of this study, mixing time was measured in microscale systems by adopting the Dual Indicator System for Mixing Time (DISMT) method, and the effects of fill volume, fluid viscosity and surface tension were investigated in 24-DSW and cylindrical geometries on a ThermoMixer with orbital diameter of 3 mm. The mixing time of the DSW showed in general the typical variation of a mixing number curve, however it was identified a range of rotational speed N=600-650 rpm, which was denoted by an increase of mixing time with speed. This phenomenon is caused by a reduced free surface oscillation over this range of speeds, which does not occur when a cylindrical geometry is considered. With a reduction of surface tension this phenomenon disappears also in the deep square wells. Mixing time measurements were also carried out in intermediate-sized reactors and compared to those obtained in lab-scale reactors by Rodriguez et al (2013, 2014). These data indicate that the natural frequency of a filled container can be used as an effective parameter to scale between microwells and larger scale shaken reactors.

Secondly, Horizontal PIV measurements were carried out in a squared shaken bioreactor with a diameter of 6.2 cm, which has the same cross-sectional area as the cylindrical reactor used by Rodriguez et al (2014). The flow in a square OSR is clearly different from what have been observed in cylindrical reactors previously. All the ensemble averaged velocity fields obtained in the square tank for a range of rotational speeds shown the effect of the four corners on fluid flow. The directions of the flow at a few phase angles were also investigated by phase-resolved PIV measurements and they were found in agreement with the flow directions in cylindrical shaken reactors. The average of the kinetic energy of a lower plane is smaller than that for a higher plane and the kinetic energy distribution also demonstrated the effects of the presence of four corners on the flow inside the square reactor.

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