STUDY ON MIXING AND SUSPENSION CHARACTERISTICS IN SINGLE-USE SHAKEN MICROWELL SYSTEMS

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The worldwide cell therapy market is growing steadily, with a growing number of therapies undergoing late-stage clinical trails. The benefits of a three dimensional environment associated with suspension bioreactor cultivation methodologies have been demonstrated using microcarrier-based expansion methods. 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 Wehiliye (2014) and a scaling law has been developed for a cylindrical geometry with internal diameters ranging from 1.5-5 cm. The aim of this work was twofold – (i) to assess the validity of the existing scaling law at the microwell scale (for internal diameters < 1.5 cm) and bridge the gap between single-use ml-scale wells and large scale conventional bioreactors and (ii) to determine the suspension characteristics and assess their impact of different parameters on the quality of the suspension. In this study, mixing time and microcarrier suspension experiments were conducted in a square well and a cylindrical well mimicking an individual well of a 24 Deep Square Well (24DSW) plate and a 24 Standard Round Well (24SRW) plate, respectively. The impact of operating conditions and fluid properties on the mixing characteristics was assessed, including fill volume, well geometry, shaken speed and orbital diameter, fluid viscosity and surface tension. It has been found that the the cylindrical well requires longer mixing time than the square one for the same fill volume at rotational speeds less than 550rpm. Comparison of the mixing time results with larger scale data (Rodriguez et al 2013, 2014) shows that mixing number decreases with Froude number and becomes constant at a lower $Fr/Fr_{critical}$ for microscale data. A small increase in mixing time was also noticed in the square well at around 600 to 650rpm and this phenomenon corresponds to a change in the shape of the liquid surface, as confirmed by visual observations. However, this phenomenon was not observed in the small-scale cylindrical well. An effect of the fluid surface tension was also observed and information on the suspension characteristics have helped elucidate the effect of scale on flow transition and particle off-bottom suspension in shaken systems.

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