Fall 10-20-2015

Engineering characterisation of a rocked-bag bioreactor to evaluate key effectors of successful mammalian cell culture

Douglas Marsh
University College London, douglas.marsh.09@ucl.ac.uk

Matthew Osborne
Eli Lilly

Martina Micheletti
University College London

Gary Lye
University College London

Recommended Citation

[1] Odeleye, A.O.O., Marsh, D.T.J., Osborne, M.D., Lye, G.J., Micheletti, M. (2014). On the fluid dynamics of a single-use stirred bioreactor. Chem. Engng. Sci., 111: 299-312.

ENGINEERING CHARACTERISATION OF A ROCKED BAG BIOREACTOR TO EVALUATE KEY EFFECTORS OF SUCCESSFUL MAMMALIAN CELL CULTURE

Douglas T. J. Marsh, Department of Biochemical Engineering, University College London, UK
douglas.marsh.09@ucl.ac.uk
Matthew D. Osborne, Eli Lilly S.A., Kinsale, Ireland
Martina Micheletti, Department of Biochemical Engineering, University College London, UK
Gary J. Lye, Department of Biochemical Engineering, University College London, UK

Key Words: Rocked bioreactor, engineering characterisation, CHO cell culture, antibody production

Engineering characterisation is essential for efficient and knowledge-led process development in biomanufacturing and to underpin the adoption of single-use technologies [1]. Despite diverse applications of rocked bag bioreactors, there is currently little understanding of the fundamental determinants of fluid mixing and mass transfer, which are important for mammalian cell culture.

In this work, a flexible single-use rocked bag bioreactor system has been fully evaluated in terms of volumetric oxygen mass transfer coefficient (k_La), CO_2 stripping rate and liquid phase mixing time (t_m) at 10, 20 and 50L scale. Five inputs were identified as potentially affecting gas transfer and mixing characteristics: rocking rate, rocking angle, fill volume, rocking acceleration and air flow rate. Based on this engineering characterisation, industrially relevant fed-batch GS-CHO cell cultures were conducted to demonstrate the effects of these parameters on cell growth, productivity and metabolite profiles.

It was found that oxygen transfer could be an issue for mammalian cell culture at the cell densities reached in industrial fed-batch processes. Within sensible operating ranges for cell culture, the oxygen mass transfer coefficient, k_La, was most sensitive to rocking rate and fill volume (5-fold higher at 25rpm compared to 15rpm). Bubble formation and the presence of a dispersed gas phase was observed at moderate rocking rates and was prevalent at high rocking rate or low fill volume. In terms of scale-up, k_La did not change significantly with a doubling in scale. In contrast, the liquid phase mixing time, t_m, approximately doubled. CO_2 stripping was largely determined by air flow rate at both 10 and 20L scales but was proportionately slower at 20L scale.

Fed-batch cultures of an industrial GS-CHO cell line producing a whole IgG were subsequently performed in a 10L rocked bags at various rocking rates. It was found that cells cultured at lower rocking rates in the absence of a dispersed gas phase had higher cell specific productivities. These results confirm the importance of k_La with regards to cell growth and antibody production and of CO_2 stripping in terms of bioreactor pH control.

[1] Odeleye, A.O.O., Marsh, D.T.J., Osborne, M.D., Lye, G.J., Micheletti, M. (2014). On the fluid dynamics of a single-use stirred bioreactor. Chem. Engng. Sci., 111: 299-312.