Sensor integration and application of a 3D-printed micro bubble column reactor for cell cultivation

H. Ostsieker 1,2, L. Frey 3, L. Jöhse 3, J. Bahnemann 3, T. Mayr 3, J. H. Grosch 3,5, R. Krull 1,2

1 Institute of Biochemical Engineering, Technische Universität Braunschweig, Germany
2 Center of Pharmaceutical Engineering (PIVZ), Technische Universität Braunschweig, Germany
3 Institute of Technical Chemistry, Leibniz University Hannover, Germany
4 Institute of Analytical Chemistry and Food Chemistry, Graz University of Technologies, Austria

PROJECT GOALS

- Novel design of micro-technologically 3D-manufactured bubble column cultivation system (µBC)
- Implementation of online measurements of biomass, DO, pH, CO2, and multiparametric online analysis
- Modular single-use concept with a user-friendly docking station
- Hydrodynamic and mass transfer characterization for reactor validation

RAPID-PROTOTYPING VIA 3D-PRINTING

- Fabrication using ink-jet like MultiJet Modeling (MJM 2500+, 3D-Systems) at TCI, University Hannover
- Accuracy of 50 µm in X-Y axes and 32 µm layer height
- High speed and flexible production compared to other micro manufacturing processes
- Different materials are printable to covering a wide range of requirements
- Reduced costs make 3D-printed single-use products favourable

3D-PRINTED MICRO BUBBLE COLUMN BIOREACTOR

- Pressurized air is supplied through a nozzle (⌀ = 0.3 mm) at the base of the µBC
- Homogenization and aeration through convective flow of bubbles
- Low volume of 550 µL offers fast heat and mass transfer characteristics
- Mixing without movable parts for increased reliability
- Online measurement of scattered light, pH, DO, CO2 and exhaust air analytics

OXYGEN TRANSFER CHARACTERISTICS

- Volumetric mass-transfer coefficient \( k_{a} \) describes the efficiency of oxygen transport into cultivation media
- Determination by dynamic gassing-out method
  \[
  OTR = \frac{dG}{dt} = \frac{k_{a}(C_{a}-C)}{u_{g}} \quad u_{g} = \frac{2D}{u_{g}}
  \]
- \( k_{a} \) increases proportionally with higher gas flow rates \( u_{g} \) → Higher oxygen transfer capacities than standard laboratory systems

SYSTEM VALIDATION WITH YEAST CULTIVATION

- Saccharomyces cerevisiae as model organism
- Diauxic growth metabolism \( \rightarrow \) Glucose and Ethanol as substrates result in two exponential growth phases

ACKNOWLEDGEMENTS

HD, LF, and RK gratefully acknowledge the financial support from the German Research Foundation (DFG) within the project Development of microreactors for biopharmaceutical applications (TR 1857/5-1). Delfin Flasch is thanked for his ongoing and profound technical support. Sarah Runke and Bernhard Mueller is thanked for providing and spotting sensor plates.

REFERENCES


DOCKING STATION

1. Connector clip with liquid inlets
2. Silicone sealing
3. 3D-printed micro-bubble column reactor (µBC)
4. Reactor sealing
5. Sensor plate
6. Frame for sensor plate
7. Docking station with integrated optical fibers, IR-Thermometer

Docking station design offers high flexibility and rapid development of 3D-printed microreactors and process development

Modular docking station design offers high flexibility and rapid development of 3D-printed microreactors and process development

ACKNOWLEDGEMENTS

HD, LF, and RK gratefully acknowledge the financial support from the German Research Foundation (DFG) within the project Development of microreactors for biopharmaceutical applications (TR 1857/5-1). Delfin Flasch is thanked for his ongoing and profound technical support. Sarah Runke and Bernhard Mueller is thanked for providing and spotting sensor plates.

REFERENCES