Zürcher Hochschule
für Angewandte Wissenschaften

Life Sciences und
Facility Management

BIOCHEMICAL ENGINEERING AND CELL CULTURE TECHNIQUE

ACTIVITIES and REFERENCE LIST

CONTACT

Prof. Dr. Ing. Regine Eibl
Zellkulturtechnik

regine.eibl@zhaw.ch

Zürcher Hochschule für Angewandte Wissenschaften
Departement Life Sciences und Facility Management
Institut für Chemie und Biotechnologie
Grüentalstrasse 14, Postfach 361
CH-8820 Wädenswil

Tel. +41 58 934 57 13
Tel. Zentrale +41 58 934 50 00
Fax Zentrale +41 58 934 50 01

www.lsfm.zhaw.ch
www.zellkulturtechnik.ch

Prof. Dr. Ing. Dieter Eibl
Bioverfahrenstechnik

dieter.eibl@zhaw.ch

Zürcher Hochschule für Angewandte Wissenschaften
Departement Life Sciences und Facility Management
Institut für Chemie und Biotechnologie
Grüentalstrasse 14, Postfach 361
CH-8820 Wädenswil

Tel. +41 58 934 57 11
Tel. Zentrale +41 58 934 50 00
Fax Zentrale +41 58 934 50 01

www.lsfm.zhaw.ch
www.bioverfahrenstechnik.ch

TRAINING FOR STUDENTS AT ZHAW

- Biotechnology: Introduction (1st term, field of study: Biotechnology)
- Biotechnology: Introduction (4th term, field of study: Food technology)
- Plant cell cultivation technique (3rd term, field of study: Biotechnology)
- Cell- and tissue cultures for pharmaceutical and medical application (4th term, field of study: Environmental engineering)
- Specialization: Cell cultivation technique (5th and 6th term, field of study: Biotechnology)
- Technical equipment and installation I and II (1st and 2nd term, field of study: Biotechnology)
- Project week: Systems engineering (3rd term, field of study: Biotechnology)
- Biochemical engineering: Basic training I and II (3rd and 4th term, field of study: Biotechnology)
- Biotechnological processes (5th and 6th term, field of study: Biotechnology)
- Specialization: Design of biotechnological production facilities (5th and 6th term, field of study: Biotechnology)
- Course “Disposables in biomanufacturing”, Master study “Life Sciences” of the Universities of Applied Sciences in Switzerland

COURSES IN FURTHER EDUCATION

- Science week (4.-8. August 2014, 3.-7. August 2015, 7.-11. August 2017, ZHAW and partners)
- Advances training course: Cell expansion and protein expression: An introduction for standard and single-use bioreactors (6.-23. August 2013, 12.-29. August 2014, 11.-28. August 2015, 9.-26. August 2016, 15. August-1. September 2017, ZHAW and partners)
- Mammalian cell-based protein expression: Upstream- and downstream-processing: From cell to bioactive substance (22. -26. April 2013 and 7.-11.April / 16.-20. June 2014, 13.-17. April 2015 and 20.-24. April / 8.-12. June 2015, 14.-18. March 2016, 12.-16. June 2017, Biotechnet Switzerland/Hoffmann-La Roche Ltd., Basel, Switzerland)
- Single-use technology (18.-19. April 2013, 9. June 2015, 14. January 2016, Master training, TU Berlin, Germany)
- Single-use systems used in biopharmaceutical production processes (8. January 2014, 13. November 2014, Master training, BOKU Vienna, Austria)
- The modern biotechnological manufacturing facility: Plastics instead glass or stainless steel (11. January 2013, 17. January 2014, 16. January 2015, Aprentas, Switzerland)
- Trends in cell cultivation techniques, cell culture bioreactors and selection criteria, bioreactor modelling (22.-24. May 2013, 7.-9. July 2014, 23.-26. June 2015, 14.-17. June 2016, 20.-23. June 2017, Master training, University of Applied Sciences Anhalt/Köthen, Germany)
- Cultivation of plant cells in standard and single-use bioreactors (21.-22. April 2016, costumized training for Nestlé, Tours, France)
- Enginnering characterisation of single-use stirred bioreactors (6.-10. June 2016, costumized, on-site training for Polpharma, Danzig, Poland

RESEARCH

- Directly financed projects by companies
- Plant cell-based compounds for the flavour and fragrance industry (Givaudan)
  07/2016-06/2017
- Development of novel single-use devives (Levitronix)
  05/2016-04/2017
- Characterization and optimization of novel single-use bioreactors (Sartorius)
  Cooperation contract
- Cultivation studies with cell culture bioreactors (Eppendorf/DASGIP)
  03/2014-12/2016
- Characterization of a new wave-mixed bioreactor system (GE Healthcare)
  08/2014-07/2015
- Optimization of plant cell bioreactors (Phyton)
  07/2014-06/2016
- Travelling Wave Bioreactor (Finesse)
  04/2011-06/2014
- CTI projects
- Innovative GMP grade biodegradable microcarrier to grow hASCSs under serum-free conditions
  01/2016-07/2018
- A small fungus with big effects
  05/2016-05/2019
- Intelligent SCADA expert system for user friendly process control (Infors)
  08/2014-07/2017
- Development of a single-use nano dose system (ReseaChem, Berner Fachhochschule BFH)
  04/2013-05/2015
- A robust CHO cell-based process platform for rapid manufacture of novel fully human bispecific monoclonal antibodies with importance for preclinical studies, immuno- and cancer therapies (NovImmune, Cell Culture Technologies and University of Zurich)
  06/2013-11/2014
- Magnetic single-use centrifugal pump (Levitronix)
  01/2012-06/2013
- Process optimization of starter cultures (Haya)
  04/2013-04/2014
- Development of a platform for scalable production of therapeutic relevant stem cells (Lonza)
  01/2012-02/2014
- Process optimization with a human hybridoma cell line for the production of a hmab for treatment of MRSA infections (Kenta)
  02/2012-04/2013
- CitsENS, a wireless disposable sensor array for disposable bioreactors (C-CIT, no lead)
  07/2012-06/2014
- EU projects
- BIOCOMES: Pesticide production with *in vitro* cultivated insect cells
  01/2014-12/2017
- glucoCell: Single-use glucose sensor for single-use bioreactors (Eurostar)
  04/2012-10/2013
- Smartcell/Green Factory (platform lead)
  01/2009-8/2013
- Projects supported by ZHAW and biotechnet Switzerland

- A novel approach for more robust and efficient biotechnological production processes with the insect cell/baculovirus expression vector system (ThermoScientific and Kühner)
  06/2016-05/2017
- A feasibility study evaluating the advantageous usage of a novel chemically defined culture medium for insect cell-based production processes in orbitally shaken single-use bioreactors
  (Cell Culture Technologies)
  08/2016-11/2016
- A new production approach for insect cell-based, biotechnological production processes (Kühner AG)
  07/2015-4/2016
- Immortalized hADSCs: An alternative to primary hADSCS for expansion and shear stress studies
  05/20015-5/2016
- Serum-free expansions and differentiations of hMSCs for therapeutical use (Cardiocentro Ticino)
  05/2014-04/2015
- Modelling of fluid flow in scaffolds used to grow epithelial cells and hMSCs (Universität Mainz)
  05/2014-04/2015
- Hairy root cultivations aimed at production of bioactive compounds (ROOTec)
  05/2014-11/2014
- Biotechnological production of rosmarinic acid in cell cultures of *Saturejah khuzistanica*: Scaling-up to benchtop bioreactor
  09/2013-06/2015
- Investigation of the influence of light on growth and secondary metabolism of plant suspension cells in single-use bioreactors (VTT)
  05/2013-12/2013
- Micromixing and cells (TU Hamburg-Harburg)
  09/2013-08/2014
- Development of a rapid test for bag materials to evaluate leachables and extractables with cell toxicity (DECHEMA)
  04/2012-12/2013
- Development of a taxol production process based on hazelnut suspension cells and single-use bioreactors (University Barcelona)
  09/2012-08/2013

JOURNAL ARTICLES

2017

- Eibl, D., Eibl, R. (2017) Flexible biomanufacturing for the production of biotherapeutics. Pharmaceutical Bioprocessing 5(1), 001-002

- Eibl, R., Eibl, D. (2017) Single-Use-Systeme in der biopharmazeutischen Produktion: Chancen und Herausforderungen. Pharmaceutical Industry 79(5), 719-724

Abstract

Single-Use-Systeme (SUS) sind sowohl bei der Entwicklung als auch kommerziellen Produktion von neuen Biotherapeutika nicht mehr wegzudenken. Es gibt sie für alle Unit Operations und wichtigen Plattformprozesse, vom Upstreamprocessing (USP) über das Downstreamprocessing (DSP) bis hin zur Formulierung und Abfüllung. Am häufigsten werden SUS aktuell für Upstreamprozesse genutzt. Der Beitrag beleuchtet ausgehend vom aktuellen Entwicklungsstand der auf dem Markt verfügbaren SUS sich abzeichnende Trends. Neben den Vorteilen werden die Limitationen der SUS sowie das zunehmende Interesse an kontinuierlichen Prozessen mit SUS kurz diskutiert und abschliessend die Typen von Single-Use-Produktionsstätten beschrieben.

2016

- Kaiser, S. C., Werner, S., Jossen, V., Kraume, M., Eibl, D. (2016). Development of a method for reliable power input measurements in conventional and single-use stirred bioreactors at laboratory scale. Engineering in Life Sciences. doi:10.1002/elsc.201600096

Abstract

Power input is an important engineering and scale-up/down criterion in stirred bioreactors. However, reliably measuring power input in laboratory scale systems is still challenging. Even though torque measurements have proven to be suitable in pilot scale systems, sensor accuracy, resolution and errors from relatively high levels of friction inside bearings can become limiting factors at smaller scales. An experimental setup for power input measurements was developed in this study by focusing on stainless steel and single-use bioreactors in the single-digit volume range. The friction losses inside the air bearings were effectively reduced to less than 0.5% of the measurement range of the torque meter. A comparison of dimensionless power numbers determined for a reference Rushton turbine stirrer (NP = 4.17±0.14 for fully turbulent conditions) revealed good agreement with literature data. Hence, the power numbers of several reusable and single-use bioreactors could be determined over a wide range of Reynolds numbers between 100 and >104. Power numbers of between 0.3 and 4.5 (for Re = 104) were determined for the different systems. The rigid plastic vessels showed similar power characteristics to their reusable counterparts. Thus, it was demonstrated that the torque-based technique can be used to reliably measure power input in stirred reusable and single-use bioreactors at the laboratory scale.

- A. Khojasteh, M.Hossein Mirjalili, J. Palazon, R. Eibl, R. M. Cusido (2016) Methyl jasmonate enhanced production of rosmarinic acid in cell cultures of *Satureja khuzistanica* in a bioreactor. Engineering in Life Sciences. doi: 10.1002/elsc.201600064

Abstract

The growing interest in rosmarinic acid (RA), an ester of caffeic acid and 3,4-dihydroxyphenyl lactic acid, is due to its biological activities,which include cognitive enhancing effects, slowing the development of Alzheimer's disease, cancer chemoprotection,and anti-inflammatory activity. Inspired by the challenge of meeting the growing demand for this plant secondary metabolite, we developed a biotechnological platform based on cell suspension cultures of *Satureja khuzistanica*. The high amounts of RA produced by this system accumulated mainly inside the cells. To further improve production, two elicitors, 100 μM methyl jasmonate (MeJA) and 40 mM cyclodextrin (CD), were tested, separately and together. MeJA increased RA productivity more than 3-fold, the elicited cultures achieving an RA production of 3.9 g L−1 without affecting biomass productivity.CDdid not have a clear effect on RA production, and under the combined treatment of MeJA + CD only a small amount of RA was released to the medium. When the cell culture was transferred from a shake flask to a wave-mixed bioreactor, a maximum RA production of 3.1 g L−1 and biomass productivity of 18.7 g L−1 d−1 was achieved underMeJA elicitation, demonstrating the suitability of *S. khuzistanica* cell suspensions for the biotechnological production of this bioactive plant secondary metabolite.

- C. Demuth, J. Varonier, V. Jossen, R. Eibl, D. Eibl (2016) Novel probes for pH and dissolved oxygen measurements in cultivations from millilitre to benchtop scale. Applied Microbiology and Biotechnology. doi: 10.1007/s00253-016-7412-0

Abstract

pH value and the concentration of dissolved oxygen (DO) are key parameters to monitor and control cell growth in cultivation studies. Reliable, robust and accurate methods to measure these parameters in cultivation systems in real time guarantee high product yield and quality. This mini-review summarises the current state of the art of pH and DO sensors that are applied to bioprocesses from millilitre to benchtop scale by means of a short introduction on measuring principles and selected applications. Special emphasis is placed on single-use bioreactors, which have been increasingly employed in bioprocess development and production in recent years. Working principles, applications and the particular requirements of sensors in these cultivation systems are given. In such processes, optical sensors for pH and DO are often preferred to electrochemical probes, as they allow semi-invasive measurements and can be miniaturised to micrometre scale or lower. In addition, selected measuring principles of novel sensing technologies for pH and DO are

discussed. These include solid-state sensors and miniaturised devices that are not yet commercially available, but show promising characteristics for possible use in bioprocesses in the near future.

- K. Blaschczok, N. Steiger, E. Jurkiewicz, U. Husemann, F. Faulstich, R. Eibl, G. Greller (2016) Evaluating a new film for single-use bags. BioProcess International 14(3) S, 26-35
- D. Eibl (2016) Einwegsysteme: Stand der Technik und sich abzeichnende Entwicklungen. GMP Journal 38, 11-12
- V. Jossen, C. Schirmer, D.M. Mostafa Sindi, R. Eibl, M. Kraume, R. Pörtner, D. Eibl (2016) Theoretical and practical issues that are relevant when scaling up hMSC microcarrier production processes. Stem Cells International doi: 10.1155/2016/4760414

Abstract

The potential of human mesenchymal stem cells (hMSCs) for allogeneic cell therapies has created a large amount of interest. However, this presupposes the availability of efficient scale-up procedures. Promising results have been reported for stirred bioreactors that operate with microcarriers. Recent publications focusing on microcarrier-based stirred bioreactors have demonstrated the successful use of Computational Fluid Dynamics (CFD) and suspension criteria (N_{S1u}, N_{S1}) for rapidly scaling-up hMSC expansions from mL- to pilot scale. Nevertheless, one obstacle may be the formation of large microcarrier-cell-aggregates, which may result in mass transfer limitations and inhomogeneous distributions of stem cells in the culture broth. The dependence of microcarrier-cell-aggregate formation on impeller speed and shear stress levels was investigated for human adipose derived stromal/stem cells (hASCs) at the spinner scale by recording the Sauter mean diameter (d_{32}) vs. time. Cultivations at the suspension criteria provided d_{32} values between 0.2 and 0.7 mm, the highest cell densities (1.25×10^6 cells mL^{-1} hASCs) and the highest expansion factors (117.0 ± 4.7 on day 7), while maintaining the expression of specific surface markers. Furthermore, suitability of the suspension criterion N_{S1u} was investigated for scalling-up microcarrier-based processes in wave-mixed bioreactors for the first time.

2015

- S.C. Kaiser, K. Blaschczok, D. Eibl (2015) Cultivation of CHO Suspension Cells and SEAP Expression in the Finesse Glass Bioreactor. BioProcess International, Industry Yearbook 2014-2015, 9
- S.C. Kaiser, N. Perepelitsa, I. Dittler, D. Eibl (2015) Experiences with a Benchtop-Scale Glass Bioreactor: Engineering Data and Cultivation Results. BioProcess International, 13(10), 46–52
- T. Fries, I. Dittler, K. Blaschczok, C. Löffelholz, W. Dornfeld, R. Schöb, A. Drews, D. Eibl (2015) Quantifizierung der hydromechanischen Beanspruchung von Pumpen auf tierische Zellen mittels des nicht-biologischen Modellsystems Emulsion. Chemie Ingenieur Technik. doi:10.1002/cite.201500126

Abstract

Zur Quantifizierung der Beanspruchung durch die Zentrifugalpumpe PuraLev® 200SU wurde der mittlere Sauter-Durchmesser des Modellsystems Emulsion in Abhängigkeit des massenspezifischen Leistungseintrages ermittelt. Anschließend wurde mit ausgewählten Parametern die Absterberate von CHO-Zellen untersucht und mit den Ergebnissen der Emulsionsversuche verglichen. Es konnte gezeigt werden, dass für das biologische System neben dem Leistungseintrag weitere Parameter wie die Impellerumfangsgeschwindigkeit Einfluss auf die Partikelbeanspruchung haben.

The shear stress in the magnetically levitated, bearingless centrifugal pump PuraLev® 200SU was determined using the Sauter mean diameter. The data was compared to CHO cell death rates at similar operating parameters. It was shown that besides the specific power input other parameters like the impeller tip speed influence the particle stress in biological systems.

- S.C. Kaiser, N. Perepelitsa, M. Kraume, D. Eibl (2015) Development of the Travelling Wave Bioreactor. Part II: Engineering Characteristics and Cultivation Results. Chemie Ingenieur Technik. doi:10.1002/cite.201500091

Abstract

The innovative travelling wave bioreactor (TWB), an orbitally shaken system, developed specifically for cell culture applications, is investigated. In this study, engineering parameters covering power input, mixing time and oxygen mass transfer obtained in two TWB prototypes are presented for the first time. Based on the results, cultivation parameters for CHO suspension cell cultivations were defined. Cell growth and substrate consumption were comparable with a wave-mixed reference bioreactor, which demonstrates the bioreactor's applicability for cultivations of mammalian cell cultures for the first time.

- S.C. Kaiser, M. Kraume, D. Eibl (2015) Development of the Travelling Wave Bioreactor. Part I: Design Studies Based on Numerical Models. Chemie Ingenieur Technik. doi:10.1002/cite.201500092

Abstract

In the travelling wave bioreactor (TWB) an orbital movement is used to set up a quasi-periodic wave motion in the partially filled, toroidal shaped vessel. Based on computational fluid dynamics (CFD) models, this study presents detailed analyses of the fluid flow in the TWB for a wide range of operational conditions. Even though the wave propagation is shown to be greatly influenced by the

rotation, it was found that the regular vessel shape facilitates a predominantly tangential flow with low back mixing, irrespective of the operational conditions. Hence, the influence of different bioreactor geometries without and with baffles is examined. The study indicates that CFD models can be used as a valuable tool for bioreactor development, because it provides a deep insight into the bioreactor's hydrodynamics and can help to reduce the number of prototypes.

- V. Jossen, C. Schirmaier, G. T. John, D. Eibl, R. Eibl (2015) On-line-pH- und DO-Messungen in Mikrocarrier-basierter hMSC-Kultur. BIOspektrum 4:422-424

  Abstract

  Spinner flasks are often used for microcarrier-based cultivations of human mesenchymal stem cells (hMSCs). Normally, they are not equipped with pH and dissolved oxygen (DO) probes. This application note describes the cultivation of hMSCs in single-use spinner flasks equipped with optical pH (SP-HP8) and DO (SP-PSt3) sensors for the first time. While reaching peak cell numbers between 4.1 x 10^7 cells and 5.9 x 10^7 cells in two cultivation runs, reliable DO and pH data were delivered.

- I. Dittler, W. Dornfeld, R. Schöb, J. Cocke, J. Rojahn, M. Kraume, D. Eibl (2015) A cost effective and reliable method to predict mechanical stress in single-use and standard pumps. J. Vis. Exp., doi:10.3791/53052

  Abstract

  Pumps are mainly used when transferring sterile culture broths in biopharmaceutical and biotechnological production processes. However, during the pumping process shear forces occur which can lead to qualitative and/or quantitative product loss. To calculate the mechanical stress with limited experimental expense, an oil-water emulsion system was used, whose suitability was demonstrated for drop size detections in bioreactors[1]. As drop breakup of the oil-water emulsion system is a function of mechanical stress, drop sizes need to be counted over the experimental time of shear stress investigations. In previous studies, the inline endoscopy has been shown to be an accurate and reliable measurement technique for drop size detections in liquid/liquid dispersions. The aim of this protocol is to show the suitability of the inline endoscopy technique for drop size measurements in pumping processes. In order to express the drop size, the Sauter mean diameter d_{32} was used as the representative diameter of drops in the oil-water emulsion. The results showed low variation in the Sauter mean diameters, which were quantified by standard deviations of below 15 %, indicating the reliability of the measurement technique.

- R. Eibl, D. Eibl (2015) Single-Use (Disposable) Systems in Biopharmaceutical Processing: Quo Vadis? ACHEMA online – Trend report No. 13, http://www.achema.de/en/press/service-for-journalists/trend-reports/trend-report-nr-13-single-use-disposable-systems-in-biopharmaceutical-processing-quo-vadis.html, 19.06.2015

  Abstract

  Single-use systems (SUS) are now used in the majority of biopharmaceutical processes involving animal cell cultures. Single-use filters, plastic storage bags, single-use mixers and single-use bioreactors for upstream processing (USP) in pre-clinical and clinical sample production are the items most commonly used. However the biopharmaceutical industry is also making greater use of SUS for downstream processing (DSP), formulation and filling. Stirred-tank single-use bioreactors for microorganisms are one of the current development priorities. There is also a need for single-use equipment to process stem cells and T-cells.

- B. Badertscher (2015) A contribution to the *in vitro* production of a gypsy moth baculovirus biopesticide. A JOUR 1: 11-13

  Abstract

  The gypsy moth (Lymantria dispar), an invasive defoliator, is controlled by a biological insecticide: the baculovirus Lyman-tria dispar multicapsid nuclear polyhedrosis virus (LdMNPV). The baculovirus is currently commercially produced in vivo. An in vitro virus production process would bring a variety of advantages. Establishing an efficient biotechnological production based on cell culture techniques was the focus of the Bachelor's thesis, and contributes to the EU project BIOCOMES (www.biocomes.eu).

- A. Gallego, I. Imseng, M. Bonfill, R.M. Cusido, Palazon, R. Eibl, E. Moyano (2015) Development of a hazel cell culture-based paclitaxel and baccatin III production process on a benchtop scale. Journal of Biotechnology, 195:93-102

  Abstract

  The growing demand for the antitumorous agent paclitaxel and the difficulty in increasing its production by genetic engineering has prompted a search for new sources of taxanes. It has been reported that taxanes can be extracted from the angiosperm *Corylus avellana* L. Our aim was to improve taxane productionby scaling up the process from mL-level to benchtop bioreactors, optimizing culture conditions andcomparing the effect of two elicitors, 1 M Coronatine (Cor) and 100 M methyl jasmonate (MeJA). Orbitally shaken flask cultures achieved a maximum fresh cell weight of 11.54 gDCW/L under control conditions, and MeJA- and Cor-treatment produced a statistically significant reduction in growth to 4.28 gDCW/L and 5.69 gDCW/L, while increasing the taxane content 3- and 27-fold, respectively. The enhancing effect of these elicitors on taxane production, despite affecting growth, was confirmed in orbitally shaken TubeSpin®Bioreactors 50, where the highest taxane content (8583.3 g/L) was obtained when1 M Cor was used and elicitation took place at a packed cell volume of 50%. Two benchtop stirred biore-actors, BIOSTAT®B plus and UniVessel®SU, were compared, the latter providing a higher biomass of *C. avellana* cell suspension cultures. Transferring the established optimum culture conditions for taxane production to the UniVessel®SU resulted in a total taxane content of 6246.1 g/L, a 10-fold increasecompared with shake flask experiments.

2014

- C. Fritz, R. Eibl, D. Müller, D. Eisenkrätzer, J. Bär, D. Eibl (2014) Single-use Bags in Zellkulturprozessen. GIT Labor-Fachzeitschrift, 12:24-26

- S. Werner, J. Greulich, K. Geipel, J. Steingroewer, T. Bley, D. Eibl (2014) Mass propagation of *Helianthus annuus* suspension cells in orbitally shaken bioreactors: Improved growth rate in single-use bag bioreactors. Engineering in Life Sciences, 14(6): 676-684, DOI:10.1002/elsc.201400024

  Abstract
  Stirred tank-bioreactors made of glass or steel, wave-mixed and orbitally shaken bag bioreactors have all proven to be suitable for the rapid development and commercial production of bioactive compounds with plant cell suspensions. Although these bag bioreactors are characterized by reduced foam formation and less flotation in comparison to stirred systems, their power input is limited. Engineering parameters such as mixing time, oxygen transfer and power input are dependent on the viscosity of the liquid and thus, investigations with plant cell suspensions are necessary. However, to save time and achieve better controllability, sodium carboxymethyl cellulose (Na-CMC) solutions in concentrations ranging from 1 to 20 $g \cdot L^{-1}$, with viscosities of between 0.005 and 0.4 Pa, were identified as appropriate model systems for mimicking plant cell suspensions with packed cell volumes (PCV) of between 30 and 70 % and similar viscosities. The current study has shown that it is possible to transfer a Helianthus annuus cell suspension process from an orbitally shaken CultiBag RM 1 L to a CultiBag RM with a 10 L working volume by adjusting the operating parameters to achieve a constant k_La value. A maximum specific growth rate μ_{max} of around 0.25 d^{-1} was achieved, which corresponds to optimized data for shake flasks and even exceeds the growth rate for stirred glass-bioreactors.

- V. Jossen, S. C. Kaiser, C. Schirmaier, J. Herrmann, A. Tappe, D. Eibl, A. Siehoff, C. van den Bos, R. Eibl (2014) Modification and qualification of a stirred single-use bioreactor for the improved expansion of human mesenchymal stem cells at benchtop scale, Pharmaceutical Bioprocessing, 2 (4):311-322

  Abstract
  To improve cultivation conditions for human bone-marrow-derived mesenchymal stem cells, we redesigned the commercially available UniVessel® SU bioreactor using results obtained from computational fluid dynamics. The goal was to produce ≥1 × 10^9 cells and to achieve expansion factors ≥30. Screening studies suggested that microcarrier solid fractions of at least 0.3% are required to reach the appropriate cell densities.
  The fluid flow pattern found in the most promising modification (#2) was altered by increasing the impeller blade angle and lowering the off-bottom clearance. As a result, the maximum required specific power input was reduced by a factor of 2.2–4.6, depending on the microcarrier concentration, and peak cell densities were 3.4-times higher than in the standard version. The peak cell number of nearly 1.1 × 10^9 cells (expansion factor = 35), which was achieved in our low-serum cultivations, indicates an improvement in the redesigned UniVessel®.

- W. Klöckner, C. Lattermann, F. Pursche, S. Werner, D. Eibl, J. Büchs (2014) Time efficient way to calculate oxygen transfer areas and power input in cylindrical disposable shaken bioreactors. Biotechnology Progress, online. DOI:10.1002/btpr.1977

  Abstract
  Disposable orbitally shaken bioreactors are a promising alternative to stirred or wave agitated systems for mammalian and plant cell cultivation, because they provide a homogeneous and well-defined liquid distribution together with a simple and cost-efficient design. Cultivation conditions in the surface-aerated bioreactors are mainly affected by the size of the volumetric oxygen transfer area (a) and the volumetric power input (P/V_L) that both result from the liquid distribution during shaking. Since Computational Fluid Dynamics (CFD)—commonly applied to simulate the liquid distribution in such bioreactors—needs high computing power, this technique is poorly suited to investigate the influence of many different operating conditions in various scales. Thus, the aim of this paper is to introduce a new mathematical model for calculating the values of a and P/V_L for liquids with water-like viscosities. The model equations were derived from the balance of centrifugal and gravitational forces exerted during shaking. A good agreement was found among calculated values for a and P/V_L, CFD simulation values and empirical results. The newly proposed model enables a time efficient way to calculate the oxygen transfer areas and power input for various shaking frequencies, filling volumes and shaking and reactor diameters. All these parameters can be calculated fast and with little computing power.

- N. Imseng, N. Steiger, D. Frasson, M. Sievers, A. Tappe, G. Greller, D. Eibl, R. Eibl (2014) Single-use wave-mixed versus stirred bioreactors for insect-cell/BEVS-based protein expression at benchtop scale, Engineering in Life Sciences, 14 (3): 264–271, DOI: 10.1002/elsc.201300131

  Abstract
  Spodoptera frugiperda-9 (Sf-9) cells used in conjunction with the baculovirus expression vector system (BEVS) represent a promising platformfor the rapid development and manufacture of protein complexes and virus-like particle (VLP) products. Several studies have described the superiority of single-use wave-mixed bioreactors although reusable stirred and, more recently, single-use stirred bioreactors have also been successfully applied. Due to their bioengineering characteristics (more homogeneous energy dissipation, reduced foam formation), wave-mixed systems are often preferred. However, a direct comparison of the influence of single-use wave-mixed and single-use stirred bioreactors on cell growth and protein expression in Sf-9/BEVS-based production processes was still lacking. We investigated Sf-9 cell growth and expression of a recombinant secreted alkaline phosphatase (rSEAP) in thewave-mixed BIOSTAT® RMaswell as the stirred UniVessel R SU and a serum-free culture medium. Irrespective of the bioreactor system, comparable

growth, substrate, and metabolite courses as well as peak cell densities (>1.2 × 107 cells mL−1) were observed in Sf-9 cell expansions performed in batch mode. Additionally, identical rSEAP quality and maximumrSEAP activities were found in biphasic productions in both bioreactor systems. Concluding, comparability of single-use wave-mixed and stirred bioreactors for insect cell culture processes was demonstrated for the first time.

- I. Dittler, St. C. Kaiser, K. Blaschczok, C. Löffelholz, P. Bösch, W. Dornfeld, R. Schöb, J. Rojahn, M. Kraume, D. Eibl (2014) A cost effective and reliable method to predict mechanical stress in single-use and standard pumps, Engineering in Life Sciences, 14(3):311-317, DOI: 10.1002/elsc.201300068

  Abstract

  The suitability of oil-water emulsions to predict shear forces in stirred bioreactors under cost-effective and time-saving conditions has been demonstrated several times, but no application to pumps has been described so far. In this report, the drop sizes in a model oil-water system were determined for the Levitronix PuraLev® MU series (PuraLev® 200MU and PuraLev® 600MU), a peristaltic pump (Masterflex® I/P Easy Load), and a 4-piston diaphragm pump (Quattroflow 1200-SU) using inline endoscopy. It was determined that the Sauter mean diameter could be used as a comparison criterion to estimate mechanical stress in pumps. The investigation showed that PuraLev® MU pumps are characterized by up to 59 % larger Sauter mean diameters than their counterparts at comparable operational conditions. This indicates lower hydrodynamic stress in the PuraLev® MU pumps. Using computational fluid dynamics (CFD), a well-streamlined fluid flow and low turbulent energy dissipation rates (TEDR) were found in the PuraLev® MU pumps, which correlated well with experimental results. A calculation model was used to predict the Sauter mean diameter by combining both experimental and CFD data. Good agreement with deviations below 13 % was determined between model predictions and experimental data.

- A. Ritala, L. Dong, N. Imseng, T. Seppänen-Laakso, N. Vasilev, S. van der Krol, H. Rischer, H. Maaheimo, A. Virkki, J. Brändli, S. Schillberg, R. Eibl, H. Bouwmeester, K. M. Oksman-Caldentey (2014) Evaluation of tobacco (*Nicotiana tabacum* L. cv. Petit Havana SR1) hairy roots for the production of geraniol, the first committed step in terpenoid indole alkaloid pathway, Journal of Biotechnology, 176C:20-28, DOI: 10.1016/j.jbiotec.2014.01.031

  Abstract

  The terpenoid indole alkaloids are one of the major classes of plant-derived natural products and are well known for their many applications in the pharmaceutical, fragrance and cosmetics industries. Hairy root cultures are useful for the production of plant secondary metabolites because of their genetic and biochemical stability and their rapid growth in hormone-free media. Tobacco (*Nicotiana tabacum* L. cv. Petit Havana SR1) hairy roots, which do not produce geraniol naturally, were engineered to express a plastid-targeted geraniol synthase gene originally isolated from *Valeriana officinalis* L. (VoGES). A SPME-GC-MS screening tool was developed for the rapid evaluation of production clones. The GC-MS analysis revealed that the free geraniol content in 20 hairy root clones expressing VoGES was an average of 13.7μg/g dry weight (DW) and a maximum of 31.3μg/g DW. More detailed metabolic analysis revealed that geraniol derivatives were present in six major glycoside forms, namely the hexose and/or pentose conjugates of geraniol and hydroxygeraniol, resulting in total geraniol levels of up to 204.3μg/g DW following deglycosylation. A benchtop-scale process was developed in a 20-L wave-mixed bioreactor eventually yielding hundreds of grams of biomass and milligram quantities of geraniol per cultivation bag.

- N. Vasilev, C. Schmitz, L. Dong, A. Ritala, N. Imseng, S.T. Häkkinen, S. van der Krol, R. Eibl, K. M. Oksman-Caldentey, H. Bouwmeester, R. Fischer, S. Schillberg (2014) Comparison of plant-based expression platforms for the heterologous production of geraniol, Plant Cell, Tissue and Organ Culture (PCTOC), 117(3):373-380, DOI : 10.1007/s11240-014-0446-z

  Abstract

  We compared the ability of different plant-based expression platforms to produce geraniol, a key metabolite in the monoterpenoid branch of the terpenoid indole alkaloid biosynthesis pathway. A geraniol synthase gene isolated from *Valeriana officinalis* (VoGES) was stably expressed in different tobacco systems. Intact plants were grown *in vitro* and in the greenhouse and were used to generate cell suspension and hairy root cultures. VoGES was also transiently expressed in *N. benthamiana*. The highest geraniol content was produced by intact transgenic plants grown *in vitro* (48 μg/g fresh weight, fw), followed by the transient expression system (27 μg/g fw), transgenic plants under hydroponic conditions in the greenhouse and cell suspension cultures (16 μg/g fw), and finally hairy root cultures (9 μg/g fw). Differences in biomass production and the duration of cultivation resulted in a spectrum of geraniol productivities. Cell suspension cultures achieved a geraniol production rate of 1.8 μg/g fresh biomass per day, whereas transient expression produced 5.9 μg/g fresh biomass per day (if cultivation prior to agroinfiltration is ignored) or 0.5 μg/g fresh biomass per day (if cultivation prior to agroinfiltration is included). The superior productivity, strict process control and simple handling procedures available for transgenic cell suspension cultures suggest that cells are the most promising system for further optimization and ultimately for the scaled up production of geraniol.

- C. Schirmaier, V. Jossen, S.C. Kaiser, F. Jüngerkes, S. Brill, A. Safavi-Nab. A. Siehoff, C. van den Bos, D. Eibl, R. Eibl (2014) Scale-up of adipose tissue-derived mesenchymal stem cell production in stirred single-use bioreactors under low-serum conditions, Engineering in Life Sciences, 14(3: 292-303, DOI: 10.1002/elsc.201300134

  Abstract

Suspension cultures, in which human mesenchymal stem cells (hMSCs) are cultivated on microcarriers in scalable single-use stirred bioreactor types, have been shown to be a promising alternative to planar flask cultures. However, stirred single-use bioreactors were originally developed for production processes with robust, permanent cell lines. hMSCs are adherent primary cells and thus expanding them in such bioreactor systems imposes more stringent requirements on bioreactor systems. For low-serum conditions (5%) and different types of stirred single-use bioreactors, a suspension criteria-based approach for expanding human adipose tissue-derived mesenchymal stem cells (hASCs) from mL- to pilot scale was successfully developed. For process scale-up, experimental and numerical investigations were performed to (1) predict optimum impeller speeds, (2) determine the main engineering parameters (local shear stress, turbulent dissipation rate, Kolmogorov microscale), and (3) verify suspension criteria N_{S1} and N_{S1u} for rapid process transfer from 100 mL to 2 L and 35 L cultures. Using optimized mediummicrocarrier combinations as well as N_{S1} and N_{S1u} as scale-up factors, total hASC quantities between $3 \cdot 10^7$ (100 mL scale) and $1 \cdot 10^{10}$ (35 L scale) were obtained. The cell quantities obtained are the highest reported to date for scalable single-use bioreactors under low-serum conditions.

- S. Werner, S. C. Kaiser, M. Kraume, Dieter Eibl (2014) Computational fluid dynamics as a modern tool for engineering characterization of bioreactors, Pharmaceutical Bioprocessing 2(1), 85-99, DOI: 10.4155/pbp.13.60

  Abstract

  Since design, construction and evaluation of bioreactors for large-scale production is costly and time consuming, computational methods may give some insights into the fluid mechanics within bioreactors. Thus, critical limiting factors, such as insufficient mixing as well as inhomogeneous nutrient and oxygen mass transfer, may be identified early in the design process. Although advanced experimental techniques such as laser Doppler anemometry and particle image velocimetry are also reliable, they are too time consuming to characterize the complete flow pattern in industrial scales and rely on optical accessibility. Therefore, the knowledge of flow characteristics provided by computational fluid dynamics (CFD) is indispensable for the rational design of bioreactors. Based on previously published reviews, the present work summarizes the latest publications on the usage of CFD to characterize and scale-up bioreactors used in biotechnological processes. Selected models that are used to predict the fluid flow pattern and key engineering parameters of commonly used bioreactors are described. Related issues, such as grid dependency of CFD results and the requirement for experimental verification are also addressed. Finally, an overview of proposed but not yet feasible CFD applications is presented, including fluid–structure interaction, the use of direct numerical simulation and the coupling fluid flow and chemical reactions.

- K. Blaschczok, C. Löffelholz, R. Eibl, D. Eibl (2014,) Combining single-use stirred bioreactor with standard cross-flow technology in biphasic protein production processes at pilot scale, Engineering in Life Sciences, 14(3):327-331, DOI: 10.1002/elsc.201300069

  Abstract

  The increasing implementation of single-use bioreactors arrived hand-in-hand with the development of new technologies contributing to increased productivity, process flexibility, and additional savings in time and costs. As a result, hollow fiber technology has recently gained renewed interest in upstream processing. Using a Chinese hamster ovary cell line in a biphasic protein production process with chemically defined minimal culture media, we combined Sartorius Stedim's BIOSTAT STR 50 L with GE Healthcare Life Sciences' reusable Hollow Fiber Cartridge CFP-6-D-55A. After a 3-day feeding growth phase, secretion of the model protein secreted alkaline phosphatase (SEAP) was introduced by replacing the growth medium with production medium using cross-flow filtration. The process was then continued and harvested as a batch with temperature shift. High cell densities exceeding 1 × 107 cells mL−1 were achieved 5 days post inoculation and maximum secreted alkaline phosphatase activities of 24 U mL−1 11 days post inoculation. Our results showed that a further decrease in processing time is possible by reducing the number of diafiltration steps from three to two.

- C. Löffelholz, S. C. Kaiser, M. Kraume, R. Eibl and D. Eibl (2014) Dynamic Single-Use Bioreactors Used in Modern Liter- and m^3-Scale Biotechnological Processes: Engineering Characteristics and Scaling Up, Advances in Biochemical Engineering/Biotechnology 138, 1-41, DOI: 10.1007/10_2013_187

  Abstract

  During the past 10 years, single-use bioreactors have been well accepted in modern biopharmaceutical production processes targeting high-value products. Up to now, such processes have mainly been small- or medium-scale mammalian cell culture-based seed inoculum, vaccine or antibody productions. However, recently first attempts have been made to modify existing single-use bioreactors for the cultivation of plant cells and tissue cultures, and microorganisms. This has even led to the development of new single-use bioreactor types. Moreover, due to safety issues it has become clear that single-use bioreactors are the “must have” for expanding human stem cells delivering cell therapeutics, the biopharmaceuticals of the next generation. So it comes as no surprise that numerous different dynamic single-use bioreactor types, which are suitable for a wide range of applications, already dominate the market today. Bioreactor working principles, main applications, and bioengineering data are presented in this review, based on a current overview of greater than milliliter-scale, commercially available, dynamic single-use bioreactors. The focus is on stirred versions, which are omnipresent in R&D and manufacturing, and in particular Sartorius Stedim’s BIOSTAT family. Finally, we examine development trends for single-use bioreactors, after discussing proven approaches for fast scaling-up processes.

- C. van den Bos, S. R. Keefe, C. Schirmaier, M. McCaman (2014), Therapeutic human cells: Manufacture for cell therapy/regenerative medicine, Advances in Biochemical Engineering/Biotechnology 138, 61-97, DOI: 10.1007/10_2013_233

  Abstract

Human primary cells (e.g. adult stem cells) as well as differentiated cells, including those of the immune system, have been found to be therapeutically useful and free of ethical concerns. Several products have received market authorization and numerous promising clinical trials are underway. We believe that such primary therapeutic cells will dominate the market for cell therapy applications for the foreseeable future. Consequently, production of such cellular products warrants attention and needs to be a fully controlled pharmaceutical process. Thus, where possible, such production should change from manufacture towards a truly scalable industrialized process for both allogeneic and autologous products. Here, we discuss manufacturing aspects of both autogeneic and allogeneic products, review the field, and provide historical context.

- R. Eibl, N. Steiger, S. Wellnitz, T. Vicente, C. John and D. Eibl (2014) Fast Single-Use VLP Vaccine Productions Based on Insect Cells and the Baculovirus Expression Vector System: Influenza as Case Study, Advances in Biochemical Engineering/Biotechnology 138, 99-125, DOI: 10.1007/10_2013-186

Abstract

During the last few years virus like particles (VLPs) have become increasingly interesting for the production of vaccines. This development is explained by their excellent safety profile as well as a significant number of clinical studies showing strong and long-lasting protection. A further reason is the possibility of speeding up VLP vaccine manufacturing by implementing single-use (SU) technology in the case of mammalian and insect-cell-based processes, for which a multitude of SU devices up to middle-volume scale already exist. After briefly introducing the vaccine types and expression systems currently in use, this chapter turns to VLP vaccines and the insect cell/baculovirus expression vector system (IC/BEVS). Based on the main process characteristics and typical process flow of IC/BEVS-based VLP vaccine productions, suitable SU devices and their implementation are addressed. We subsequently report on the successful development of a fast, scalable benchtop production process generating a four-protein component influenza A H1N1 VLP vaccine candidate. This process is based on Spodoptera frugiperda (Sf)-9 cells and combines Redbiotec's rePAXTM technology with obtainable SU devices for upstream (USP) and downstream processing (DSP).

2013

- J. Olownia, S. Werner, D. Eibl (2013), Plant and Animal Suspension Cell Cultures: Scale-up of Geometrically Dissimilar Orbitally Shaken Single-Use Bioreactor, Genetic Engineering & Biotechnology News 33(21)
- S.C. Kaiser, D. Eibl (2013) Single-use Pumpen in der Prozesstechnologie. ChemieXtra, 10-2013. 30-31
- S.C. Kaiser, K. Blaschczok, D. Eibl (2013) Novel CHO Suspension Cell Cultivation: Studying Cellular Growth and SEAP Expression in the Finesse SmartGlass Bioreactor, Genetic Engineering & Biotechnology News 33(14), 32 – 33, DOI:10.1089/gen.33.14.17
- S.C. Kaiser, K. Blaschczok, D. Eibl (2013) Cultivation of CHO Suspension Cells and SEAP Expression in the Finesse Glass Bioreactor, BioProcess International 11(7), 30
- M.I. Georgiev, R. Eibl, J.-J. Zhong (2013) Hosting the plant cells in vitro: recent trends in bioreactors, Applied Microbiology and Biotechnology 97(9), 3787-3800, DOI: 10.1007/s00253-013-4817-x

Abstract:

Biotechnological production of high-value metabolites and therapeutic proteins by plant in vitro systems has been considered as an attractive alternative of classical technologies. Numerous proof-of-concept studies have illustrated the feasibility of scaling up plant in vitro system-based processes while keeping their biosynthetic potential. Moreover, several commercial processes have been established so far. Though the progress on the field is still limited, in the recent years several bioreactor configurations has been developed (e.g., so-called single-use bioreactors) and successfully adapted for growing plant cells in vitro. This review highlights recent progress and limitations in the bioreactors for plant cells and outlines future perspectives for wider industrialization of plant in vitro systems as "green cell factories" for sustainable production of value-added molecules.

- N. Lehmann, H. Rischer, D. Eibl, R. Eibl (2013) Wave-Mixed and Orbitally Shaken Single-Use Photobioreactors for Diatom Algae Propagation, Chemie Ingenieur Technik 85 (1-2), 197 – 201, DOI: 10.1002/cite.201200137

Abstract

Although vertical column, flat-plate, tubular, bubble column and airlift photobioreactors are widely used for the cultivation of diatoms, it has been shown that bubble-induced hydrodynamic stress created in these types of bioreactor can damage cells. Therefore, three single-use surface-aerated bag bioreactors, known for their outstanding results in cultivating shear-sensitive mammalian cells, were for the first time investigated for their suitability in growing the model microalgae Phaeodactylum tricornutum. All of the systems, which were additionally aerated with CO2 and equipped with illumination systems providing different light qualities, guaranteed a 22- to 43-fold increase in cell density within seven days, without any addition of cell protection agents or changes in cell morphology. Maximum cell density and dry biomass were achieved in the orbitally shaken 2D-bag by using cool-white fluorescent tubes.

- N. Steiger, R. Eibl (2013) Interlaboratory Test for Detection of Cytotoxic Leachables arising from Single-Use Bags, Chemie Ingenieur Technik 85 (1-2), 26 – 28, DOI: 10.1002/cite.201200171

Abstract
An interlaboratory test for detection of cytotoxic leachables arising from single-use bags was established and performed. Results from cultivations with two bag materials indicate that leachables influencing cell growth and metabolism were secreted. For the other seven bag materials a migration of leachables can be excluded.

- C. Löffelholz, U. Husemann, G. Greller, W. Meusel, J. Kauling, P. Ay, M. Kraume, R. Eibl, D. Eibl (2013) Bioengineering Parameters for Single-Use Bioreactors: Overview and Evaluation of Suitable Methods, Chemie Ingenieur Technik 85 (1-2), 40 – 56, DOI: 10.1002/cite.201200125
  Abstract
  During the past five years, the number of single-use bioreactors used in biopharmaceutical research and production has increased tremendously. This increase has been particularly associated with mammalian cell culture processes from small- to medium-scale volumes. Even though nowadays customers can choose from a multitude of 2nd and 3rd generation single-use bioreactors, ranging from mL- up to m3-scale, there is a lack of knowledge of their engineering parameters. Different approaches have been applied to characterization investigations, resulting in an inability to compare different single-use bioreactors with each other and their reusable counterparts, creating an obstacle to a systematic approach to scaling-up the process. This article describes parametric, experimental and computer-based numeric methods for biochemical engineering characterization of single-use bioreactors, which have already been used successfully for the characterization of their reusable counterparts. For the first time, these methods have been evaluated in terms of their practical application.

- S.C. Kaiser, M. Kraume, D. Eibl (2013) Development of the Travelling Wave Bioreactor – A Concept Study, Chemie Ingenieur Technik 85 (1-2), 136 – 143, DOI: 10.1002/cite.201200127
  Abstract
  This study presents the concept of the travelling wave single-use bioreactor, based on an orbitally shaken, annular-shaped vessel. A numerical model was developed for early design studies in order to reduce the number of prototypes. The flow characteristics in two different vessel shapes were investigated. It was shown that the orbital motion combined with the toroidal shape of the bioreactor create the desired wave characteristics in the contents of the vessel.

- S. Werner, J. Olownia, D. Egger, D. Eibl (2013) An Approach for Scale-Up of Geometrically Dissimilar Orbitally Shaken Single-Use Bioreactors, Chemie Ingenieur Technik 85 (1-2), 118 - 126, DOI: 10.1002/cite.201200153
  Abstract
  An initial approach for scaling up geometrically dissimilar orbitally shaken bioreactors is presented. A novel ShakerBag Option for Multitron Cell shaking incubators allows a rapid increase in working volume from small TubeSpin bioreactors or shake flasks up to 10 L, thus offering a simple and cost-efficient alternative to present systems for scale-up. The engineering parameters for scale-up of the orbitally shaken single-use bags were determined using traditional methods. Modern computational fluid dynamics based methods were used to gain a deeper insight into the fluid flow behavior. Furthermore, mass propagation of plant cell suspensions (Nicotiana tabacum and Vitis vinifera), as well as cell expansion and production of protein complexes using insect cells (Sf-9), show the potential of orbitally shaken single-use bags.

- K. Blaschczok, S.C. Kaiser, C. Löffelholz, N. Imseng, J. Burkart, P. Bösch, W. Dornfeld, R. Eibl, D. Eibl (2013) Investigations on Mechanical Stress Caused to CHO Suspension Cells by Standard and Single-Use Pumps, Chemie Ingenieur Technik 85 (1-2), 144 – 152, DOI: 10.1002/cite.201200135
  Abstract
  Mechanical stress caused to transfected Chinese hamster ovary (CHO) suspension cells by reusable and single-use magnetically levitated, bearingless centrifugal pumps was investigated. Cell death rates were determined for different pump speeds and compared with data from a peristaltic and a 4-piston diaphragm pump. Furthermore, the fluid distribution inside the PuraLev® 200 pump was modeled using computational fluid dynamics. The results reveal considerably lower mechanical stress to CHO cells caused by the magnetically levitated bearingless centrifugal pumps than by the peristaltic and diaphragm pump.

- S.C. Kaiser, V. Jossen, C. Schirmaier, D. Eibl, S. Brill, C. van den Bos, R. Eibl (2013) Fluid Flow and Cell Proliferation of Mesenchymal Adipose-Derived Stem Cells in Small-Scale, Stirred, Single-Use Bioreactors, Chemie Ingenieur Technik 85 (1-2), 95 – 102, DOI: 10.1002/cite.201200180
  Abstract
  The fluid flow and suspension characteristics inside small-scale, stirred, single-use bioreactors were investigated experimentally and by means of computational fluid dynamics. The required impeller speeds for homogenous suspension were determined for two microcarrier types. The shear stress level and turbulence distribution were predicted using a numerical model, which was verified by particle image velocimetry measurements. In subsequent cultivations of primary mesenchymal adipose-derived stem cells, up to 31.4-fold expansion in cell number was achieved for serum concentrations as low as 5 %.

BOOKS AND BOOK CHAPTER

2017

- S. Werner, R. W. Maschke, D. Eibl, R. Eibl (2017) Bioreactor Technology for Sustainable Production of Plant Cell-Derived Products. In: Pavlov A, Bley, T (eds.), Bioreactor Technology for Sustainable Production of Plant Cell-Derived Products, 1-20, Springer. ISBN: 978-3-319-32004-5, DOI: 10.1007/978-3-319-32004-5_6-1

Abstract

The successful cultivation of plant cell and tissue cultures for the production of valuable chemical components requires the selection of an appropriate bioreactor. Selection criteria are determined based on a number of factors that are intrinsic to particular plant cell or tissue cultures and are influenced by the process objectives. Due to the specific properties of plant cell and tissue cultures, bioreactor systems may differ significantly from those used for microorganism or animal cell cultures. Furthermore, the differences from one plant culture to another can be immense; it is obvious that the optimal bioreactor system for a plant suspension cell culture is different to one for a plant tissue culture in many ways.

General considerations are presented, and based on these key points, selection criteria are used to establish a “bioreactor chooser” tool. The particular details of the most relevant bioreactor types for plant cell and tissue cultures are listed and described.

To produce valuable products, the process also needs to be scaled up to an economically justifiable size, which is usually done either by scaling up the size of the bioreactor itself or by bioreactor parallelization. Therefore, the most significant influencing factors are also discussed..

2016

- V. Jossen, R. Eibl, R. Pörtner, M. Kraume, D. Eibl (2016) Stirred bioreactors: Current state and developments, with special emphasis on biopharmaceutical production processes. In: Larroche C, Sanroman MA, Du G, Pandey A (eds.), Bioprocesses, bioreactors and controls. Part 2: bioreactors for industrial processes, 179-216,Elsevier. ISBN: 9780444636638

Abstract

It is undisputed that stirred bioreactors are the most common type of bioreactors for submerged bioprocesses. Stirred bioreactors for biopharmaceuticals representing the strongest growing branch of modern biotechnological products are the focus of our chapter. They are available in working volumes from mL- up to 70 m^3 and used for a wide range of expression systems that require aseptic conditions.

Based on a brief summary of some basic rules for the construction and operation of stirred bioreactors, this chapter will review the key engineering issues that affect aseptic stirred bioreactor design. We will also provide readers with some general information on transport phenomena in stirred bioreactors, before discussing special design aspects and performance parameters for expression systems (mammalian and microbial cells) that prevail in commercial biopharmaceutical production processes. Special attention will be paid to single-use stirred bioreactors, which may have advantages over their re-usable counterparts and have become widely-accepted over the past years.

- B. Badertscher, R. Eibl, D. Eibl (2016) Single-Use-Technologie von A-Z. DECHEMA. http://a-z-singleuse.org/
- W. Meusel, C. Löffelholz, U. Husemann, T. Dreher, G. Greller, J. Kauling, D. Eibl, S. Kleebank, I. Bauer, R. Glöckler, P. Huber, W. Kuhlmann, G.T. John, S. Werner, S.C. Kaiser, R. Pörtner, M. Kraume (2016) Recommendations for process engineering characterization of single-use bioreactors and mixing systems by using experimental methods. DECHEMA. ISBN: 978-3-89746-171-0 http://dechema.de/dechema_media/SingleUse_ProcessEngineeringCaracterisation_2016-p-20001485.pdf

2015

- V. Jossen, R. Eibl, D. Eibl (2015) Numerische Strömungsuntersuchungen für die Massstabsübertragung der Expansion von humanen mesenchymalen Stammzellen in gerührten Single-Use Bioreaktoren. 17. Köthener-Rührer-Kolloquium 2014, 29- 43, ISBN 978-3-86011089-8

Abstract

Aufgrund des hohen Potentials von humanen mesenchymalen Stammzellen (hMSC) für therapeutische Anwendungen werden neben geeigneten Kultivierungssystemen Methoden für die schnelle Massstabsübertragung (Scale-Up) benötigt. Dabei liegt der aktuelle Fokus auf gerührten Single-Use Bioreaktoren, in welchen die hMSC auf Microcarriern (MC) expandiert werden. In der vorliegenden Arbeit wurden 2 Vertreter von gerührten Single-Use Bioreaktoren, der Corning® Spinner und der BIOSTAT® STR 50L, mittels numerischer Fluiddynamik (Computational Fluid Dynamics CFD) verfahrenstechnisch untersucht, und geeignete Bedingungen für die Kultivierung mesenchymaler Knochenmarksstammzellen (hBM-MSC) definiert. Diese Untersuchungen bilden die Grundlage für die nachfolgend realisierte Massstabsübertragung vom Spinner auf den gerührten Pilotbioreaktor. Die numerischen Untersuchungen zeigten, dass bei den ermittelten NS1- und NS1u- Kriterium in beiden Kultivierungssystemen vergleichbare verfahrenstechnische Bedingungen (Scherbelastung, spezifischer Leistungseintrag) vorlagen, wobei nach 7 Tagen Kultivierungen mit einer einmaligen Feedzugabe eine Gesamtlebendzellzahl von $3.58 \cdot 10^{10}$ hMSC pro Batch (V 50L) erreicht wurde. Dies entspricht einer Lebendzelldichte

von 7.16·105 Zellen mL-1, die zu den höchsten bisher in der Fachliteratur beschriebenen Werten für hMSC-Produktionen mit MC bei nur 5% Serumeinsatz gehört. Eine Zelldifferenzierung konnte durch flowyztometrische Untersuchungen ausgeschlossen werden.

- S. C. Kaiser, D. Eibl, R. Eibl (2015) Single-use bioreactors for animal and human cells. In: Al-Rubeai M (ed.), Animal cell culture. Cell Engineering 9, 445-499, Springer Cham: DOI: 10.1007/978-3-319-10320-4

  Abstract

  Single-use (SU) bioreactors are being increasingly used in productionprocesses based on animal (i.e. mammalian and insect) and human cells. They are particularly suitable for the production of high-value products on small and mediumscales, and in cases where fast and safe production is a requirement. Thus, it is notsurprising that SU bioreactors have established themselves for screening studies,cell expansions, and product expressions where they are used for the production of pre-clinical and clinical samples of therapeutic antibodies and preventive vaccines. Furthermore, recent publications have revealed the potential of SU bioreactors for the production of cell therapeutics using human mesenchymal stem cells (hMSCs). This chapter provides a perspective on current developments in SU bioreactors and their main applications. After briefly introducing the reader to the basics of SU bioreactor technology (terminology, historical milestones and characteristics compared to their reusable counterparts) an overview of the categories of currently available SU bioreactor types is provided. SU bioreactor instrumentation is then examined, before discussing well-established and novel applications of SU bioreactors for animal and human cells. This includes descriptions of the engineering characteristics of often-used types of SU bioreactors, covering wave-mixed, stirred, orbitally shaken systems and fixed-bed systems. In this context, the scaling-up of geometrically and non-geometrically similar SU bioreactors is also addressed.

2014

- V. Jossen, R. Pörtner, S. Kaiser; M. Kraume, D. Eibl, R. Eibl (2014) Mass production of mesenchymal stem cells – Impact of bioreactor design and flow conditions on proliferation and differentiation. In: Eberli D (ed.), Regenerative Medicine and Tissue Engineering, InTech. ISBN 978-953-51-4114-3

- N. Lehmann, I. Dittler, M. Lämse, A. Ritala, H. Rischer, D. Eibl, K.M. Oksman-Caldentey, R. Eibl (2014) Disposable bioreactors for the cultivation of plant cell cultures. In: Paek KY, Murthy HN, Zhong JJ (eds.), Production of biomass and bioactive compounds using bioreactor technology, 17-46, Springer Berlin. DOI: 10.1007/978-94-017-9223-3_2

  Abstract

  The trend for using disposable bioreactors in modern biotechnological processes has also been adopted for plant cell cultivations. In fact, plant cell cultures are now being grown in disposable bioreactors with volumes up to 400 L. This trend has been witnessed for both the development and commercial manufacture of therapeutic proteins, secondary metabolite-based pharmaceuticals and cosmetic compounds. Prominent examples of commercial products are Protalix's ELELYSO and Mibelle Biochemistry's Phyto Cell Tech-derived bioactive compounds.

  This chapter discusses the current state of disposable bioreactor technology for plant cell cultures. After a brief introduction to the general fundamentals of disposable bioreactors (relevant technical terms, advantages and limitations of disposable bioreactors) a current overview of disposable plant cell bioreactors and their instrumentation will be provided. We will describe the working principles and engineering characteristics of disposable bioreactor types that are scalable and successfully being used for the cultivation of plant cell suspension and hairy root cultures. In addition, we will provide selected application examples focusing on the cultivation of geraniol producing tobacco cells. The chapter will end with perspective on future developments of disposable bioreactor technology for plant cell cultures.

- R. Eibl, N. Steiger, C. Fritz, D. Eisenkrätzer, J. Bär, D. Müller, D. Eibl (2014) Recommendation for leachables studies: Standardized cell culture test for the early identification of critical films for CHO cell lines in chemically defined culture media. DECHEMA. ISBN: 978-3-89746-149-9 http://www.dechema.de/dechema_media/SingleUse_Leachables_2014_en-p-4734.pdf

- N. Imseng, S. Schillberg, C. Schürch, D. Schmid, K. Schütte, G. Gorr, D. Eibl, R. Eibl (2014) Suspension culture of plant cells under heterotrophic conditions. In: Meyer HP, Schmidhalter DR (eds.) Industrial scale suspension culture, 225-257, Wiley Blackwell. DOI: 10.1002/9783527683321.ch07

  Abstract

  Plant cell culture technology (PCCT) provides an environmentally friendly and controlled method to produce secondary metabolites, and recombinant proteins (e.g. enzymes, antibodies and vaccines). These molecules having importance in medicine, food industry and cosmetics are expressed in heterotrophic growing plant cell suspension cultures in the majority. After presenting an overview of commercial products based on plant cell culture processes, this chapter will focus on plant cell suspension cultures, process and bioreactor designs which have proven to be useful for successful growing them up to large scale. Two case studies describing the usage of the plant stem cell line PhytoCellTec™Malus Domesticus cv. Uttwiler Spätlauber for cosmetic purposes and the manufacture of the pharmaceutical molecule paclitaxel highlight latest improvements in PCCT and discuss costs and regulatory aspects from manufacturer`s view. At the end a view on the development of heterotrophic plant cell fermentation will be given.

- R. Eibl, C. Löffelholz, D. Eibl (2014) Disposable bioreactors for inoculum production and protein expression. In: Pörtner R (ed.), Animal cell biotechnology: Methods and protocols, methods in molecular biology. Vol. 1104, 265-284, Humana Press. DOI: 10.1007/978-1-62703-733-4_18

  Abstract

  Disposable bioreactors have been increasingly implemented over the past ten years. This relates to both R & D and commercial

manufacture, in particular, in animal cell-based processes. Among the numerous disposable bioreactors which are available today, wave-mixed bag bioreactors and stirred bioreactors are predominant. Whereas wave-mixed bag bioreactors represent the system of choice for inoculum production, stirred systems are often preferred for protein expression. For this reason, the authors present protocols instructing the reader how to use the wave-mixed BIOSTAT CultiBag RM 20 L for inoculum production and the stirred UniVessel SU 2 L for recombinant protein production at benchtop scale. All methods described are based on a Chinese hamster ovary (CHO) suspension cell line expressing the human placental secreted alkaline phosphatase (SEAP).

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PH.D. THESIS

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- S. Kaiser (2015) Characterization and optimization of single-use bioreactors and biopharmaceutical production processes using Computational Fluid Dynamics, Ph.D. thesis, TU Berlin, Germany

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- C. Löffelholz (2014) CFD as a tool for engineering characterization of single-use bioreactors and for scaling-up processes for establishing and producing biotherapeutics, Ph.D. thesis, BTU Cottbus, Germany

ORAL PRESENTATIONS

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- I. Wolfgram, L. Lisica, R. Lombriser, P. Neubauer, R. Eibl, D. Eibl (2017) Perfusion-based production of inoculum cultures for large volume cell banks, Continuous Biomanufacturing, Oxford, England, 06/2017
- S. Werner, D. Eibl (2017) Characterization, qualification, usage of modern CFD methods, and a general bioreactor overview from an academic point of view, ACTIP Meeting, Gdansk, Poland, 05/2017
- R. W. Maschke, M. Stalder, S. Werner, E. Abellan, D. Eibl (2017) Multivariate process transfer and scale-up models for mammalian cell cultures, DECHEMA Himmelfahrtstagung - Models for Developing and Optimising Biotech Production, Neu-Ulm, Germany, 05/2017
- V. Jossen (2017) Standardized expansion of human adipose tissue-derived stromal/stem cells (hASCs) in wave-mixed single-use bioreactors with one-dimensional motion. ECI: Single Use Technologies II: Bridging Polymer Science to Bioprocess Applications, Tomar, Portugal, 05/2017
- S. Werner (2017) Strömungsmechanische Untersuchungen zur Auslegung und Übertragung von biotechnologischen Prozessen, ProcessNet Fachtagung Mischprozesse und CFD, Dresden, Germany, 03/2017
- R. Eibl (2017) Single-use Technologien in derbiopharmazeutischen Produktion: Vom USP bis zum Fill&Finish. Pharma Kongress Düsseldorf, Germany, 03/2017
- S. Werner (2017) Process and bioreactor development and optimization by means of Computational Fluid Dynamics, IQPC: Disposable Solutions for Biomanufactoring, Munich, Germany, 02/2017

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- D. Eibl (2016) Single-Use Technologien in der biopharmazeutischen Produktion: Vom USP bis Fill&Finish, 8. Konferenz Single-Use-Disposables 2016, Concept Heidelberg, Heidelberg,Germany, 11/2016
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- R. W. Maschke, G. T. John, D. Eibl (2016) Potential von Sensor Spots für Single-Use Systeme im Labormassstab. 18. Heiligenstädter Kolloquium – Technische Systeme für die Lebenswissenschaften, Heilbad Heiligenstadt, Germany, 09/2016
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- K. Blaschczok, I. Dittler, D. Eibl, R. Eibl (2016) In-process control of insect cell- and baculovirus-based r-protein production processes using Cedex Analyzers, 2nd Cedex Analyzer User Days, Mannheim, Germany, 09/2016
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- S. Werner (2016) Engineering parameters: measurement and relevance, Workshop: Built Your Own Culture Monitoring Device Today, A3P Bioproduction, Brussels, Belgium, 05/2016
- S. Werner, M. Stalder, C. Vontobel, A. Castan, D. Eibl, R. Eibl (2016) Engineering characterization and cultivation of fast growing plant suspension cells using the ReadyToProcess WAVE™ 25 bioreactor system

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- R. Eibl (2016) Single-use technologies in biopharmaceutical production: An overview from USP to fill&finish. 2016 Pharma Congress Düsseldorf (Germany), 04/2016
- R. Eibl (2016) Issues that are relevant when scaling-up hMSC microcarrier production processes in stirred bioreactors. BioProScale Symposium 2016, Berlin (Germany), 04/2016
- R. Eibl (2016) A single-use bioreactor-based approach for the scalable expansion of human mesenchymal stem cells. BIOTECH WORLD 2016, Moscow (Russia), 03/2016
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- I. Dittler (2015) Mechanical stress in standard and single-use pumps using cell- and particle-based stress analysis, BioProcess International, Boston (USA), 10/2015
- V. Jossen (2015) Successfully employing single-use bioreactors for different expression systems, ECI Conference, Leesburg VA (USA), 10/2015
- I. Dittler (2015) Evaluierung der mechanischen Beanspruchung von Pumpen auf ein nicht-biologisches Modellsystem, Rührerkolloquium Köthen „Mischvorgänge in Bioprozessen", Köthen (Germany) 06/2015
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- I. Dittler, W. Wolfgang (2015) New low shear force single-use pump system enables high cell viabilities, protein activities and a safe, pulsation free conveyance of sensitive biotech media, Biopharmaceutical Development & Production (BDP), Los Angeles (USA), 03/2015
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- V. Jossen, S. Kaiser, A. Ott, A. Siehoff, S. Brill, G. Greller, A. Tappe, R. Eibl, D. Eibl (2014) Optimization of a bench-top single-use bioreactor for the expansion of adipose-tissue and bone marrow derived human mesenchymal stem cells, 41st Annual ESAO Congress, Rome (Italy), 09/2014
- V. Jossen, S. Kaiser, A. Siehoff, C. van den Bos, D. Eibl, R. Eibl (2014) A successful approach in order to rapidly scaling-up microcarrier-based expansions of human mesenchymal stem cells for allogeneic therapies, 3rd International Conference on Tissue Science & Regenerative Medicine, Valencia (Spain) 09/2014
- T. Dreher, C. Löffelholz, G. Greller, U. Husemann, D. Eibl (2014) Charakterisierung und Einsatz der gerührten single-use Bioreaktor-Baureihe BIOSTAT STR in der pharmazeutischen Industrie, Rührerkolloquium Köthen „Massstabsübertragung in gerührten Behältern", Köthen (Germany), 06/2014
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- S. Werner, S.C. Kaiser, M. Kraume, D. Eibl (2013) Neue Bioreaktor-Konzepte mit orbital-geschüttelter Bewegung, ProcessNet Jahrestreffen der Fachgruppen Kristallisation und Mischvorgänge, Magdeburg, (Germany), 03/2013

APPLICATION NOTES AND SCIENTIFIC REPORTS

- C. Löffelholz, N. Imseng, R. Eibl, D. Eibl, S. Rosemann, K.H. Scheibenbogen (2015) CHO cell-based production of a secreted model protein using the novel BIOSTAT A
- V. Jossen, A. Ott, A. Siehoff, C. van den Bos, D. Eibl, R. Eibl (2015) Microcarrier-based expansion of hBM-MSCs in the BIOSTAT CultiBag STR 50L: An approach for allogeneic therapies
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- C. Löffelholz, K. Blaschczok, I. Dittler, N. Lehmann, S.C. Kaiser, D. Eibl, P. Bösch, R. Schöb (2014) Investigations into Mechanical Stress Caused to CHO Suspension Cells by Single-use Magnetically Levitated, Bearingless Centrifugal Pumps
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REVIEWS FOR

- Applied Microbiology and Biotechnology
- Engineering in Life Sciences
- Pharmaceutical Bioprocessing
- Biotechnology Progress
- Biotechnology and Bioengineering
- Biotechnology and Applied Biochemistry
- Phytochemistry Reviews
- Plant Cell Reports
- Journal Biotechnology