Application of microfluidics for the development of intensified aminotransferase (ATA) processes

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Development of biocatalytic processes is greatly dominated by well-established batch process based screening technologies, e.g. glass vials (mL) and microtiter plates (μL). However, there is still a need for improvement of currently available technologies and for new technologies enabling relatively easy screening and characterization of different process options. For example, small-scale microfluidic platforms enable testing of complex process options, by combining multiple process steps in a plug-and-play manner, that are difficult to assess with conventional methods. Early in the development of biocatalytic processes, most attention is given to developing and modifying the biocatalyst to reach required process targets. However, it is important to consider the downstream processing (DSP) early in the process development as well, i.e. the downstream costs and limitations to the separation steps will greatly influence the economic viability due to the constraints placed on the required process metrics. This thesis will therefore emphasise product recovery limitations and requirements in combination with the biocatalyst performance and limitations. Here the focus is mainly related to biocatalytic processes where it is found beneficial/necessary to implement in-situ co-product/product removal (IScPR/ISPR). For example, through combined operation of reactor and separation modules, as such applications require selective separation and sufficient driving force to influence the process significantly.

In recent years, many microfluidic applications have proven useful for process and synthesis development within the area of organic synthesis, i.e. flow chemistry. For example, the unique characteristics of the small scale enable safer and efficient handling and production of explosive and/or toxic compounds. Furthermore, development based on applying microfluidic platforms potentially enables easier introduction of continuous process aspects, when suitable. The motivation for this project is to investigate the potential of applying microfluidic technologies in the development and testing of biocatalytic processes. Within this thesis, microfluidic modules are applied as tools to screen, characterize, and test reactor and separation process options. Furthermore, multiple microfluidic modules are combined in order to test complex process configurations, i.e. reactor modules combined with separation modules, as a means of narrowing down and optimizing the most promising process options.

Throughout this thesis the applicability of microfluidics, as an integrated part of biocatalytic process development, is evaluated based on case studies focusing on the asymmetric synthesis of chiral amines using aminotransferases (ATAs). Chiral amines are valuable building blocks for many pharmaceuticals and precursors. The application of ATAs for asymmetric synthesis has many advantages, but it is also common that there are some challenges. In many cases it is found beneficial/necessary to apply various process engineering strategies, e.g. IScPR and ISPR, to overcome the challenges and ensure the economic feasibility of such processes. With economic process feasibility in mind, it can be extremely useful to apply microfluidic platforms to enable fast screening and characterization of various process options in order to overcome the challenges. Due to the physicochemical properties of the compounds involved in the case studies in this thesis, the focus will be on the application/development of liquid-liquid extraction modules to operate in combination with reactor modules. The main outcome of this PhD thesis is knowledge on the potential of applying microfluidics, in combination with conventional methods, for the development of biocatalytic processes. More specifically, microfluidics will enable testing of complex process options and strategies, which are very difficult to test with conventional methods, by combining microfluidic modules representing different process steps in a plug-and-play manner. The advantages and technology constraining disadvantages of microfluidics for biocatalytic process development are both identified in this thesis. Novel applications of microfluidic development of ATA processes are investigated in detail, i.e. first by characterization of single microfluidic process steps (reactor and liquid-liquid extraction modules) and afterwards by testing of complex processes by combining multiple microfluidic process steps. This is realized by putting in place a microfluidic demonstration system, a plug-and-play combination of a reactor module with two liquid-liquid extraction modules and settlers. Another novelty of this thesis, is the application of the integrated liquid-liquid extraction steps to both recover the product, using in-situ product removal (ISPR), and at the same time feed the main substrate, i.e. in-situ substrate supply (ISSS). Furthermore, guidelines for identifying suitable ISPR/IScPR options – and, importantly, for eliminating unfeasible options – for ATA processes are proposed.

General information
Publication status: Published
Organisations: Department of Chemical and Biochemical Engineering, CAPEC-PROCESS
Contributors: Heintz, S.
Number of pages: 199
Publication date: 2015

Publication information
Place of publication: Kgs. Lyngby
Publisher: Technical University of Denmark (DTU)
Original language: English
Electronic versions:
602626_DTU_PhD_S_ren_trykt_fil_1.pdf
Source: PublicationPreSubmission
Source-ID: 115503679