Stereospecific Production of Hydrophobic Compounds with Immobilized Biocatalysts in Stirred Tank Reactors

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Introduction

Stereoselective synthesis of fine chemicals, pharmaceuticals and agrochemicals imply high economic potential. Enzymes catalyze various chemical reactions with high selectivity. Hence, they gain more and more importance for production processes. The enzymatic production of hydrophobic compounds is still challenging due to the instability of such biocatalysts in organic solvents, which are required for an improved conversion. The research project aims at the development of a technical solution for the production of chiral, hydrophobic compounds with immobilized biocatalysts. Key entity within the project was a temperature sensitive hydrogel as reversible immobilization matrix, which allows the sequential loading, repetitive use and unloading of the hydrogel (Fig. 1).

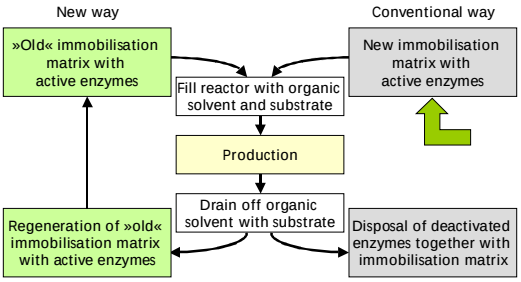

Fig. 1: The concept of the „new“ way for the process

Approach and Results

The approach can be divided into the following steps:

- Production and optimization of hydrophilic gels for the admission of enzymes and adaptation of the characteristics in consideration of the requirements from process- and reaction engineering.
- Production of the immobilized biocatalyst and definition of the reaction conditions.
- Investigation of the immobilized biocatalyst in a laboratory-scaled reactor including the definition of the process parameters and the development of a process control concept
- Determination of the reaction kinetics and development of a simulation tool for the description of this new process on the basis of an existing plant simulator (WinZPR).

Hydrophilic Gels

The developed hydrophilic gels (NIPA-based) are suitable as an embedding matrix for the selected enzyme system. For an acceptable enzyme loading time, these gels must be modified with PEG. The disadvantage of this modification is a loss of the mechanical stability, which makes the integration of a supporting matrix and the use of a sleeve necessary (Fig. 2). Beyond that the investigations show that the phase transition temperature of the gels can be increased by addition of ionic comonomer, whereby their functionality can be adapted to a possibly rising reaction temperature.

Fig. 2: Hydrophilic Gel

Enzymatic Reaction System

The suitability of the developed hydrogels was examined using a model enzyme system. The carbonyl-reductase from *Candida parapsilosis* can convert a multiplicity of acetophenone derivatives to chiral alcohols. The results show that the immobilzation within the hydrogel increases the biocatalyst stability in an organic solvent. Comparative investigations with PVA immobilized biocatalyst show good agreements concerning the reaction parameters and higher productivities.

Process Development

A production process is designed based on a standard stirred tank reactor as commonly used in small and middle sized companies specialized in the field of fine chemicals. Main emphasis is put on the internal regeneration of the immobilization matrices. Because of their sticky behaviour and their softness they need aspecial handling in the reactor environment. Furthermore a dosing strategy for the Substrat was developed.

Simulation Tool

Further Investigations aimed at the development of a software tool, which can be used by small and medium sized enterprises (SME) for projecting new plants or for the optimization of existing plants. For this purpose a model describing partitioning equilibria and kinetics on immobilization matrix level and a biochemical reaction model were linked together and integrated in an existing process simulation tool (WinZPR). First simulation results show a good agreement with the experimentally determined data.

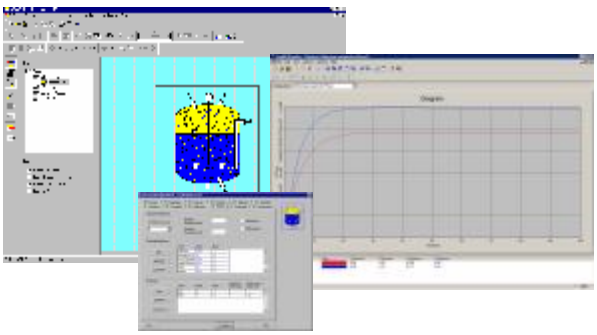

Fig. 3: Software tool WinZPR

Conclusion

A two phase enzymatic production process is shown with a new kind of immobilization matrix that allows an integrated reprocessing. For a simple adaptation, the designed production process is based on standard reactor equipment. A mathematical model, integrated in an existing process simulation tool, supports a better understanding and subsequent optimization of the process.

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