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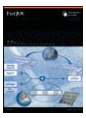

Biocatalysis

Heterogeneous Catalysts "on the Move": Flow Chemistry with Fluid Immobilised (Bio)Catalysts

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Abstract: As both, continuous synthesis and (bio-)catalysis gained increasing interest in research as well as for industrial applications, ways for merging these fields enables novel opportunities for modern sustainable process development. In this contribution, an alternative approach for the application of immobilized enzymes in continuous flow processes is presented utilizing heterogeneous biocatalysts as a mobile phase. Based on superabsorber-entrapped enzymes and whole cells as a "fluid heterogeneous phase", a segmented hydrogel/organic solvent system was developed. Its applicability was investigated with two entirely different model reaction systems, namely the alcohol dehydrogenase (ADH)-catalysed reduction of acetophenone, and the aldoxime dehydratase (Oxd)-catalysed dehydration of octanal oxime. In particular for solvent labile catalytic systems, this approach offers an alternative for the application of immobilized biocatalysts in a continuously running process beyond the "classic" packed bed and wall coated reactors.

Introduction

Over the past years, flow chemistry has gained increasing interest in academia as well as industry.[1–4] As pointed out from regulatory agencies such as the FDA or EMA, one desired key feature of such continuous flow processes in the pharmaceutical industry is to ensure a constant product quality.[5,6] In particular the combination of extremely selective catalysis and continuous manufacturing can yield high-quality products with high reliability. As these kinds of systems offer advantages over classical batch processes, this research area flourishes.[1–4] When it comes to the use of catalysis in flow, in particular heterogenized catalysts turned out in many cases as a preferred form of the catalysts due to, e.g., increased stability and simple separation from the product mixture. However, at the same time applications with such heterogeneous catalysts are surprisingly limited to a few established concepts. The most prominent ones of them are visualized in Figure 1 and briefly summarized in the following.[7]

Packed bed reactors are among the most popular and successfully applied systems.[8,9] One major drawback of the immobilized, and therefore often highly modified catalysts, is the limitation to very stable catalysts. In addition, technical disadvantages like pressure drops, which might complicate scale-up enormously, are known. Monolithic reactors are another commonly used method for the application of heterogeneous catalysts in microreactor chemistry. However, the technique does not significantly differ from packed bed reactors, except for the usually much smaller diameter of the reactor tube.[10] Yet another method is coating[11,12] and modification of the reactor wall surface or even the use of a catalytic active metal as reactor material. Recently, copper-catalyzed click reactions have been employed in a copper tube, which acts as a catalyst.[13] Coated wall reactors are also commonly used for several biocatalytic systems.[14]

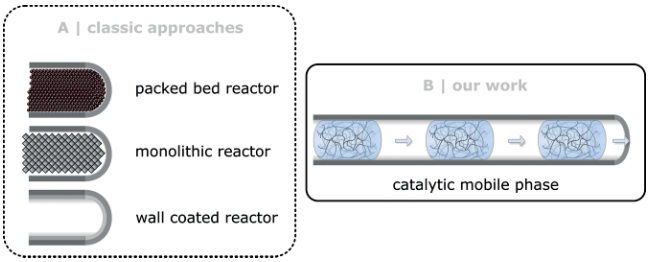

Figure 1. Approaches for application of immobilized catalysts in flow mode. A: Standard approaches such as packed bed, monolithic, or wall coated reactors. B: Our approach based on catalytic hydrogel segmented flow.

A major limitation of all such types of heterogeneous catalysts in flow is their applicability only for very stable catalytic systems. When catalysts lose activity over a certain operating time, constant product quality cannot be ensured. Especially biocatalysts can suffer in terms of stability, particularly in the presence of organic solvents.[15] Exceptions for extremely long-term stable biocatalysts are, e.g., lipases like the widely applied lipase from *Candida antarctica* B (CAL-B), which can be used in organic solvents.[16,17]

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