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Biocatalytic oxidase: Batch to continuous

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ABSTRACT

The adoption of more efficient development strategies and manufacturing techniques will be essential for future success in the bio manufacturing sectors. Continuous operation of biocatalytic processes has the potential to offer many advantages over established batch process methodologies. There exist opportunities for improved process control; ease of scale up; minimizing of interruptions in production; reducing reactor size; and economic use of biocatalysts.

The Coflore™ Agitated Cell Reactor (ACR) is a dynamically mixed plug flow reactor. The Coflore design employs a patented mixing technique where free moving agitators within each reaction stage promote mixing when the reactor body is subjected to lateral shaking. Multiple discrete (interlinked) reaction cells give good mixing and plug flow, and the design permits the use of slurries and handling of gas/liquid mixtures. The Coflore Agitated Tube Reactor (ATR) is an industrial tube flow reactor for homogenous and two phase fluids. Employing the same mixing principle as the lab scale Coflore ACR, it uses lateral movement to generate mixing and stage separation to prevent back mixing.

We describe the application of these continuous plug flow reactors for bioprocess development starting from simple lab scale batch processes; through benchtop plug flow reactors (ACRs); and on to the multi-litre production scale agitated tube reactor (ATR). The presentation will compare the results of an oxidation reaction catalysed by D-amino acid oxidase (DAAO) operated under batch and continuous conditions, and will illustrate how application of the ACR and ATR reactors can facilitate process development.

Keywords: Biocatalysis; Continuous flow; BIOCHEMIST; Coflore; Oxidase; Multiphase

1. Introduction

With a strong trend for automation in pharmaceutical research, high-throughput chemistry is still carried out in batches; whereas flow-through processes are restricted to production processes (Jas and Kirschning, 2003). Unlike batch reactors, the output of a flow device can be changed without altering the hardware or set-up conditions. This flexibility saves time and cost in development. The main advantages of the continuous approach are facile automation, reproducibility, safety and process reliability as reaction parameters are more easily controlled. The improved control capabilities of flow systems can also deliver better yield and productivity (Fig. 1). A fully optimised flow process can be used to continually synthesise complex products in a single process from inexpensive and simple starting materials, a task unparalleled by batch chemistry methods (Bartrum et al., 2010; Baxendale et al., 2006; Bogdan et al., 2009; Benito-Lopez et al., 2008).

Traditionally, flow systems have been considered unable to handle multiphase systems and long reaction times efficiently. Continuous flow processes are complemented by current trends in modern synthetic chemistry as they can be performed using immobilised catalysts or reagents (Ley and Baxendale, 2002; Drewry and Coe, 1999). Many continuous-flow processes are already established in synthetic chemistry (Ley et al., 2006), however, the uses of flow reactors in bio applications are still limited with only a handful reported in the literature (Coughlin et al., 1975).

The use of microreactors, Mason et al. (2007) has been widely reported in academia and yet only relatively recently has it been reported describing their industrial use (Markowz et al., 2005). In these types of reactor laminar flow dominates

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