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## Comparison of the biocatalytic performances of immobilized nitrilase in milli-scale reactors for continuous production of nicotinic acid

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### PURPOSE OF THE ABSTRACT

Continuous bioreactor context

Enzyme immobilization strategies are being actively investigated by the scientific community. In addition to the obvious interest of re-use of the biocatalyst, it is also essential for process intensification with integration of continuous operations [1]. Flow catalysis is indeed highly coveted by industrials to maximize the productivity but represent a major challenge. In this regard, the pharmaceutical industry has expressed its willingness to move from their traditional batch production to a continuous operating mode [2]. Promising technologies with high scaling potential due to their maturity are packed bed reactors (PBR) and wall immobilized enzyme reactors. Miniaturization at microscale for better mixing conditions have been the privileged option for wall immobilized enzyme reactors [3]. However, sizing up and numbering up should be combined to mitigate the complexity and cost of the heating and pumping apparatus at industrial scale [4]. With the reactor size increase, the geometry need to be optimized to maintain the mixing efficiency.

Experimental results

In this context, we immobilized a commercial nitrilase (specific activity measured at 1.1 U/mg) in a milli-scale reactor (i.e. characteristic dimension of 1mm) shaped with a pillar geometry. The reactor surface is coated with a thin layer of silica microbeads (i.e. total volume loss less than 10%) for higher loading capacity. The biocatalytic performances are compared to those obtained with a milli-size PBR [5]. For fair comparison between the two technical solutions, the biocatalytic performances are assessed once the outlet conversion is around 50%.

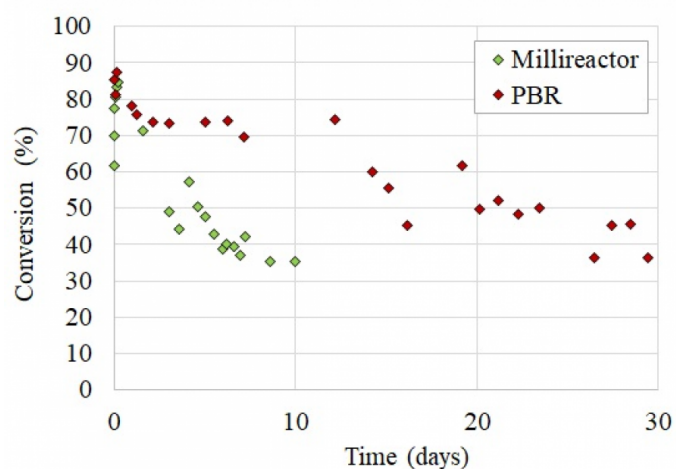
In the milli-pillar reactor, the specific productivity is higher than in the PBR (Table 1) meaning that the ratio of useful immobilized enzymes is higher. However, the total turnover is not as high as the one obtained with the PBR because of sharper decrease of the outlet conversion with time (Figure 1). This difference in the immobilized enzyme stability may be explained by the change in the immobilization strategy (i.e. protocol, bead size and bead chemical composition). The kinetic impact of these choices will be investigated for cleared understanding of the different behaviours obtained with each technology. It has to be noted that using a milli-structured reactor allows to reduce the pumping power (i.e. theoretical pressure drop at least 50% higher for PBR than those measured with milli-structured reactor). This operating characteristic can be one of the fundamental criteria for choosing a technology, especially when process scaling-up is considered.

## □□Geometry optimization with scale-up perspectives

Change in reactor structure will be experimentally studied by applying similar immobilization protocol and operating conditions to a zigzag milli-reactor (fluid volume of 0.51 mL). Computational fluid dynamics (CFD) using Comsol software are in progress and aim at combining mass transfer, laminar flow and Michaelis-Menten surface reaction equations. The objective is to understand the influence of the reactor characteristic dimensions as well as of the internal structure modifications on the outlet conversion. Optimum geometry choices based on modelling results would allow testing an experimental multi-stage up-scaling. The final goal of the project is to treat a pilot-scale throughput of 1 L/h.

## FIGURES

	PBR	Milli-pillar
Liquid flowrate (ml.min <sup>-1</sup> )	0.03	0.04
Void volume (mL)	0.45	0.57
Time (days) / cycles number	23d / 2234	5d / 561
Specific productivity ( $\mu\text{mol}/\text{min}/\text{mg}$ )	0.10	0.16
TTN (g. g enz <sup>-1</sup> )	405	128



**FIGURE 1**

Table 1

Biocatalytic performances of the PBR and surface coated milli-pillar reactor - Calculated metrics once the outlet conversion is at 50%

**FIGURE 2**

Figure 2

Biocatalytic conversion of the PBR and milli-pillar shaped reactor over time

## KEYWORDS

Flow processes | Wall enzyme immobilization | Process intensification | Bioreactor

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