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Editorial

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Current Development in Biocatalysis: Biocatalyst Engineering

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Modern drug manufacturing faces both ecological and economic challenges. Catalyst, one of the key components in the synthesis of active pharmaceutical ingredients (APIs), also plays a crucial role in the production pipeline. Although being used widely in industrial process, transition-metal catalysts still seem both costly and inefficiently, owing to the expense and toxicity of metals [1]. The emphasized "green" and sustainable chemistry nowadays requires improvement and revolution in the pharmaceutical industry. Sheldon's environmental factor [2], also known as E-factor, defined as the mass ratio of waste against product in a chemical process, is one of the gauges assessing the process ecology. Based on Sheldon's analysis, the E-factor of pharmaceutical processes are 25-100, comparing to 0.1 of oil refining and <1-5 of bulk chemical production.

Biocatalysis, taking advantage of natural or crafted enzymes, has its own beauty in directing chemical reactions. Produced from cell culture, enzyme have the potential of catalyzing the chemical reactions with remarkable chemo-, regio- and stereo-selectivity. This advantage may reduce the E-factor by not only turning over substrates to products at higher yield, but also avoiding the use of protecting and deprotecting reagents [3]. In 2008, Pfizer has incorporated lipolase biocatalysis in the synthetic pipeline of Pregabalin; the E-factor was reduced to 17 from previous 86 [4]. In addition, the enzymes work in biological conditions - physiological temperature and pH, ambient temperature, environment-benign solvent. The biocatalytic conditions are therefore simpler, more efficient, less risky, and "greener" [5].

The biocatalysis was not a hot topic until the technology development like metagenomics, bioinformatics, protein and metabolic engineering, and high-throughput screening [6]. Rational designs and standardized development and production of biocatalysts have become faster and more efficient. An enzyme is modeled, optimized and produced based on specific type of reaction they are to catalyze: oxidation, reduction, hydrolysis, or C-C/C-N bond formation. Once produced from cell line, the enzyme biocatalyst may work in several ways, depending on the phase where it stays.

Whole cell biocatalysis was prevailing about a decade ago, for ease in use and free of complicated purification [7]. The cellular membrane serves as a natural filter separating the product from the enzyme and cofactor; the cofactor, on the other hand, is regenerated by the cells. However, the limitation of the whole-cell systems is also obvious. The cell membrane acts as a barrier limiting the diffusion of the substrates and products, slowing down (or even stopping when in lack of membrane transportation mechanism of unnatural molecules) the reactions [8]. Side reactions catalyzed by other enzymes in cells reduce the selectivity of the target reactions. In addition, the reaction and production rates may also be inhibited by cell regulation. In a word, whole cell catalysis restricts and complicates the catalytic chemistry, due to its intrinsic complexity.

Isolation of the enzyme from the cells is another option to produce biocatalyst. Removing the cell environment takes away the diffusional barrier, side-reaction potentials and reaction inhibition, and thus improves the reaction rate and selectivity. However, extra cost in purification of single-use biocatalysts is a new concern. In order to overcome this inherent disadvantage, biocatalyist engineering aiming to heterogenize the homogeneous reactions has long been investigated [9]. Besides the capability of being recycled, the stability of the heterogenized enzymes is also improved against heat or organic solvents. Coating enzyme onto surface of silica or resin is a common way of immobilization, partially inspired by the success of heterogeneous chemical catalysts [10]. But the large volume and mass of the supporting material of silica or resin significantly decrease the enzymatic concentration. Cross-linked enzyme aggregate (CLEA) is an alternative heterogenization strategy: first add ammonium sulfate to precipitate enzymes as aggregates, and then introduce linker molecules to cross-link between enzyme molecules inside aggregates. CLEAs with smaller particle sizes have higher surface areas and hence better activity, but are harder to be separated by filtration. The introduction of magnetic nanoparticles into CLEA matrix (mCLEA) makes further improvement, by allowing magnetic separation of the heterogeneous catalyst.

The development of biocatalyst engineering shows promising progress, but still needs considerable efforts. As the platform carrying the active enzyme molecules, biocatalyst systems require protein engineering in order to enhance the performance and versatility. Cofactor selection and recycling is another challenge for industrial application of biocatalysis [11]. In addition, selection of solvent and reagent, and reactor engineering are also crucial in development of biocatalytic systems.

In conclusion, emergence and development of genetic, biological and chemical techniques have allowed accessible biocatalysis for pharmaceutical industry. Biocatalyst, as one of the crucial component of biocatalysis, has been developed and engineered to achieve better performance. Extracted enzymes reduce the limitation from nature, and improve reusability by immobilization. Future development shall continuously be guided by process ecology, and focus on development and engineering of catalytic matrices and environment, including cofactors, solvents, reagents and reactions.

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